JAN

Access DB# 82122

# SEARCH REQUEST FORM

**Scientific and Technical Information Center**

Requester's Full Name: Samuel Weilin Examiner #: 79120 Date: 12-4-02
Art Unit: 1653 Phone Number 306-3413 Serial Number: 09/800,856
Mail Box and Bldg/Room Location: 9801 Results Format Preferred (circle): (PAPER) DISK E-MAIL
OR 9D06

**If more than one search is submitted, please prioritize searches in order of need.**

**********

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: _____

Inventors (please provide full names): _____

_____

Earliest Priority Filing Date: 3-5-2001

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**

please search peptide structure in Claim 1, the limitations set forth in claims 2-4 as well (see the attachment).

thanks.

Sam Lin.

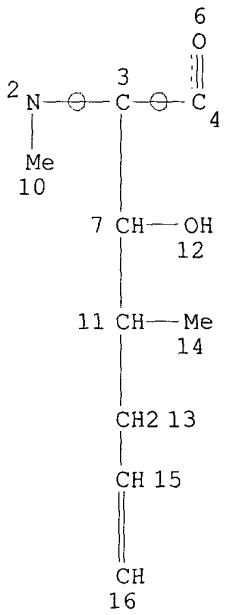
Jan Delaval
Reference Librarian
Biotechnology & Chemical Library
CM1 1E07 – 703-308-4498
jan.delaval@uspto.gov

**********

| STAFF USE ONLY | | Type of Search | | Vendors and cost where applicable | |
|---|---|---|---|---|---|
| Searcher: | | NA Sequence (#) | | STN | ✓ |
| Searcher Phone #: | 306-4498 | AA Sequence (#) | | Dialog | |
| Searcher Location: | | Structure (#) | ✓ | Questel/Orbit | |
| Date Searcher Picked Up: | 12/6/02 | Bibliographic | | Dr.Link | |
| Date Completed: | 12/12/02 | Litigation | | Lexis/Nexis | |
| Searcher Prep & Review Time: | | Fulltext | | Sequence Systems | |
| Clerical Prep Time: | 30 | Patent Family | | WWW/Internet | |
| Online Time: | + 80 | Other | | Other (specify) | |

PTO-1590 (8-01)

```
=> fil reg
FILE 'REGISTRY' ENTERED AT 15:34:17 ON 12 DEC 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2002 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   11 DEC 2002  HIGHEST RN 475975-25-8
DICTIONARY FILE UPDATES:  11 DEC 2002  HIGHEST RN 475975-25-8

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d sta que l37
L7            21 SEA FILE=REGISTRY ABB=ON  PLU=ON  (100364-58-7/BI OR 122547-85-
                 7/BI OR 172222-30-9/BI OR 223415-64-3/BI OR 457612-98-5/BI OR
                 457612-99-6/BI OR 457613-00-2/BI OR 457613-01-3/BI OR 457613-02
                 -4/BI OR 457613-03-5/BI OR 457613-04-6/BI OR 457613-05-7/BI OR
                 457613-06-8/BI OR 457613-07-9/BI OR 457613-08-0/BI OR 457613-09
                 -1/BI OR 457613-10-4/BI OR 457613-11-5/BI OR 59865-13-3/BI OR
                 624-48-6/BI OR 96-33-3/BI)
L8            17 SEA FILE=REGISTRY ABB=ON  PLU=ON  L7 AND SQL/FA
L9                STR
```

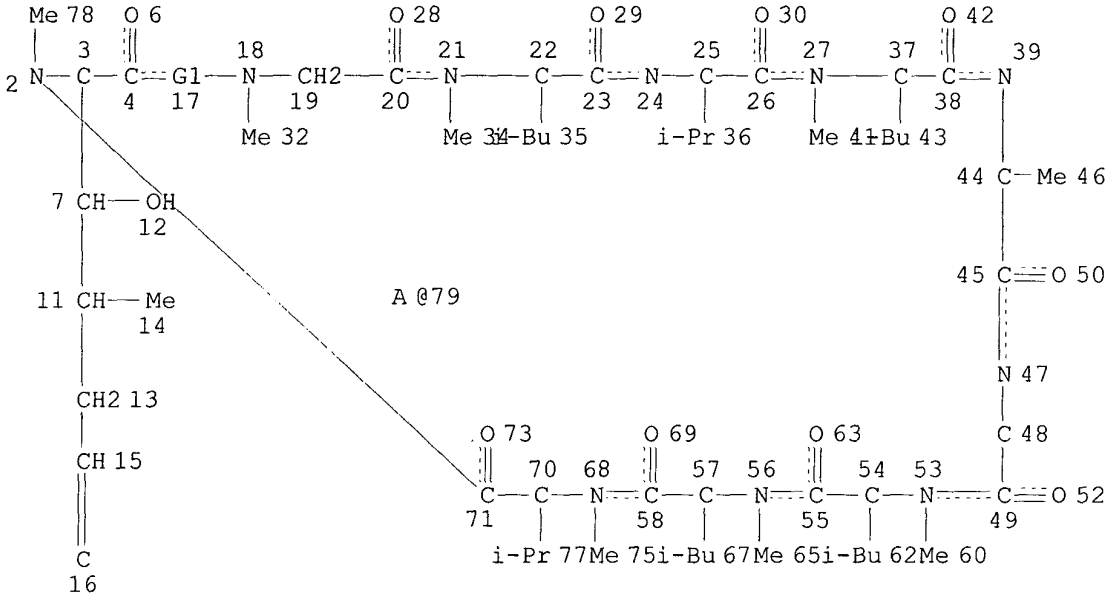



Jan Delaval
Reference Librarian
Biotechnology & Chemical Library
CM1 1E07 - 703-308-4498
jan.delaval@uspto.gov

```
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED
```

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 12

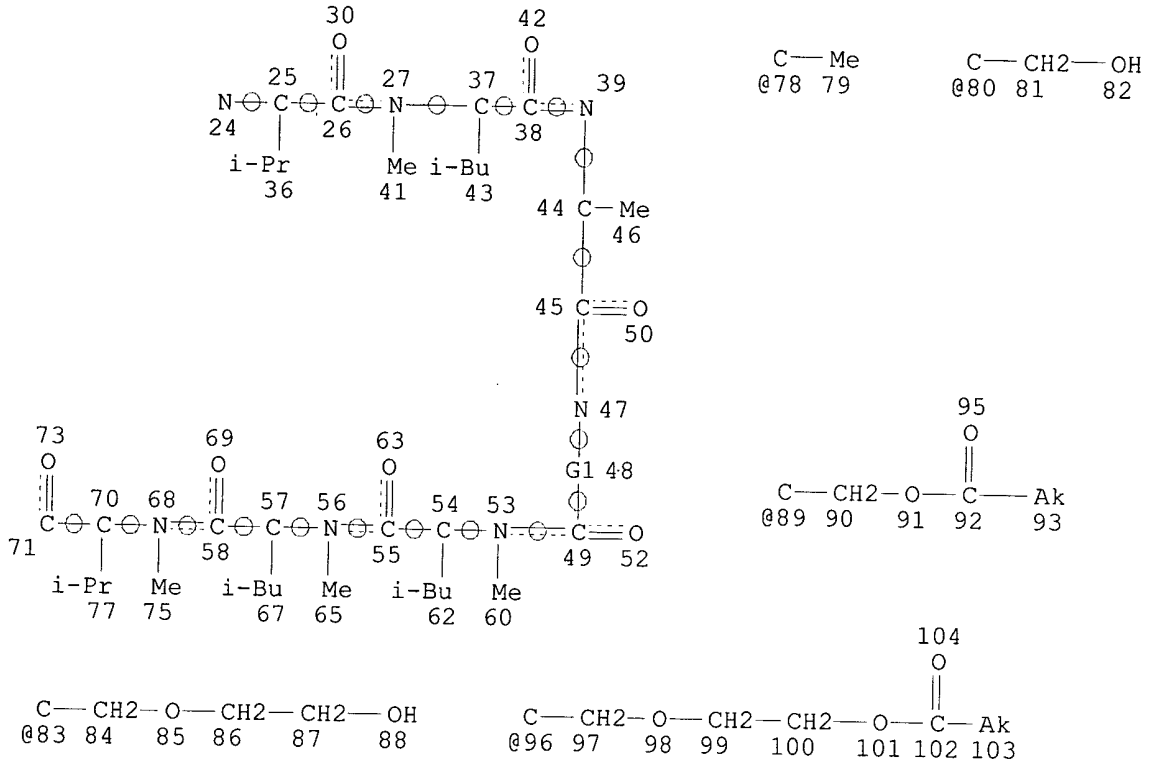
STEREO ATTRIBUTES: NONE
L11 685 SEA FILE=REGISTRY SSS FUL L9
L12 727 SEA FILE=REGISTRY ABB=ON PLU=ON ['ABU''NVA'VT]'SAR'LVLA[AS]LL V/SQSP
L13 342 SEA FILE=REGISTRY ABB=ON PLU=ON L11 AND L12
L14 342 SEA FILE=REGISTRY ABB=ON PLU=ON L13 AND 11/SQL
L15 STR




REP G1=(3-10) 79
NODE ATTRIBUTES:
CONNECT IS M1 RC AT 16
CONNECT IS M1 RC AT 48
CONNECT IS M1 RC AT 79
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 63

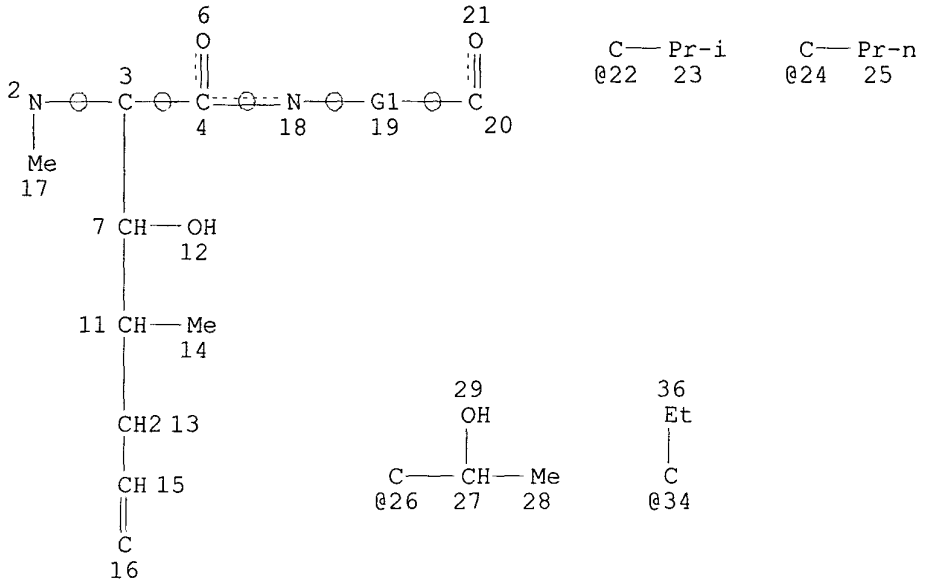
STEREO ATTRIBUTES: NONE
L17 224 SEA FILE=REGISTRY SUB=L14 CSS FUL L15
L18 STR



VAR G1=78/80/89/83/96
NODE ATTRIBUTES:
CONNECT IS M1 RC AT 24
CONNECT IS M1 RC AT 71
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 64

STEREO ATTRIBUTES: NONE
L20 166 SEA FILE=REGISTRY SUB=L17 CSS FUL L18
L25 STR




VAR G1=34/22/26/24
NODE ATTRIBUTES:
CONNECT IS M1 RC AT 2
CONNECT IS M1 RC AT 16
CONNECT IS M1 RC AT 20
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 26

STEREO ATTRIBUTES: NONE

L26 126 SEA FILE=REGISTRY SUB=L20 SSS FUL L25
L27 11 SEA FILE=REGISTRY ABB=ON PLU=ON L26 AND (LABELED OR IDS/CI OR (D OR T)/ELS OR 11C# OR 13C# OR 14C# OR C11# OR C13# OR C14#)
L28 115 SEA FILE=REGISTRY ABB=ON PLU=ON L26 NOT L27
L29 27 SEA FILE=REGISTRY ABB=ON PLU=ON L28 AND NC>=2
L30 21 SEA FILE=REGISTRY ABB=ON PLU=ON L28 AND NR>=3
L31 82 SEA FILE=REGISTRY ABB=ON PLU=ON L28 NOT (L29 OR L30)
L32 1 SEA FILE=REGISTRY ABB=ON PLU=ON L31 AND MULTICHAIN/NTE
L33 81 SEA FILE=REGISTRY ABB=ON PLU=ON L31 NOT L32
L34 65 SEA FILE=REGISTRY ABB=ON PLU=ON L33 NOT L8
L35 12 SEA FILE=REGISTRY ABB=ON PLU=ON L34 AND (C64H113N11O15 OR C69H114N12O17 OR C68H116N12O16 OR C65H115N11O15 OR C64H113N11O16 OR C64H113N11O14)
L36 4 SEA FILE=REGISTRY ABB=ON PLU=ON L35 NOT (101531-57-1/BI OR 101531-89-9/BI OR 158805-69-7/BI OR 158805-72-2/BI OR 158805-75-5/BI OR 158805-76-6/BI OR 158851-25-3/BI OR 220871-49-8/BI)
L37 3 SEA FILE=REGISTRY ABB=ON PLU=ON L36 NOT 158805-81-3/BI

=> d his

(FILE 'HCAPLUS' ENTERED AT 14:18:09 ON 12 DEC 2002)
DEL HIS
E OR Y/AU
L1 105 S E4-E8

```
                E LAZAROVA T/AU
L2           30 S E3-E11
                E ENANTA/PA,CS
L3           13 S E3-E9
L4          137 S L1-L3
L5            5 S L4 AND ?CYCLOSPOR?
                SEL DN AN 1 2
L6            2 S L5 AND E1-E4
                SEL RN

     FILE 'REGISTRY' ENTERED AT 14:21:00 ON 12 DEC 2002
L7           21 S E5-E25
L8           17 S L7 AND SQL/FA
L9              STR
L10          32 S L9
L11         685 S L9 FUL
                SAV L11 LIU800/A
L12         727 S ['ABU''NVA'VT]'SAR'LVLA[AS]LLV/SQSP
L13         342 S L11 AND L12
L14         342 S L13 AND 11/SQL
L15             STR L9
L16          11 S L15 CSS SAM SUB=L14
L17         224 S L15 CSS FUL SUB=L14
                SAV L17 LIU800A/A
L18             STR L15
L19           9 S L18 CSS SAM SUB=L17
L20         166 S L18 CSS FUL SUB=L17
                SAV L20 LIU800B/A
L21             STR L9
L22             STR L21
L23           0 S L22 SAM SUB=L20
L24           2 S L22 FUL SUB=L20
L25             STR L22
L26         126 S L25 FUL SUB=L20
                SAV L26 LIU800C/A
L27          11 S L26 AND (LABELED OR IDS/CI OR (D OR T)/ELS OR 11C# OR 13C# OR
L28         115 S L26 NOT L27
L29          27 S L28 AND NC>=2
L30          21 S L28 AND NR>=3
L31          82 S L28 NOT L29,L30
L32           1 S L31 AND MULTICHAIN/NTE
L33          81 S L31 NOT L32
L34          65 S L33 NOT L8
L35          12 S L34 AND (C64H113N11O15 OR C69H114N12O17 OR C68H116N12O16 OR C
                SEL RN L35 2 5 7-12
L36           4 S L35 NOT E26-E33
                SEL RN 4
L37           3 S L36 NOT E34
L38          20 S L8,L37
                SAV L38 LIU800D/A

     FILE 'HCAOLD' ENTERED AT 15:32:02 ON 12 DEC 2002
L39           0 S L38

     FILE 'USPATFULL, USPAT2' ENTERED AT 15:32:05 ON 12 DEC 2002

     FILE 'REGISTRY' ENTERED AT 15:32:24 ON 12 DEC 2002
                SEL RN L8 17
L40          16 S L8 NOT E35

     FILE 'HCAPLUS' ENTERED AT 15:32:57 ON 12 DEC 2002
L41          29 S L40 OR L37
L42           1 S L41 AND L4
```

L43 28 S L41 AND (PD<=20010305 OR PRD<=20010305 OR AD<=20010305)
L44 29 S L41-L43

FILE 'USPATFULL, USPAT2' ENTERED AT 15:33:58 ON 12 DEC 2002
L45 3 S L40 OR L37

FILE 'REGISTRY' ENTERED AT 15:34:17 ON 12 DEC 2002

=> d sqide can tot l37

L37 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2002 ACS
RN 442912-25-6 REGISTRY
CN Cyclosporin A, 6-[(2S,3R,4R,6E)-10-[(2,5-dioxo-1-pyrrolidinyl)oxy]-3-hydroxy-4-methyl-2-(methylamino)-10-oxo-6-decenoic acid]- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 11
NTE cyclic
modified (modifications unspecified)

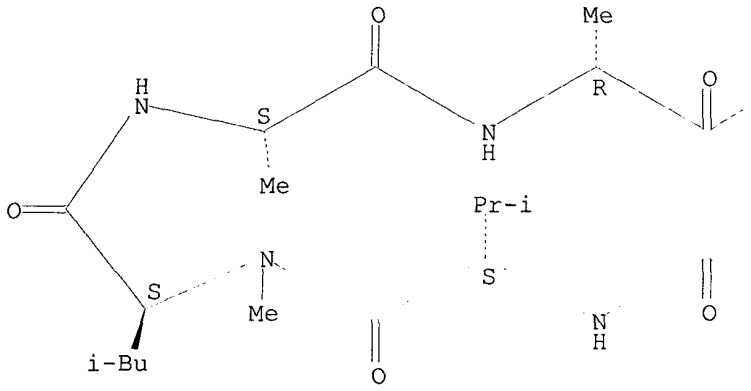
| type | ------ location ------ | | description |
|---|---|---|---|
| uncommon | Aaa-1 | - | - |
| uncommon | Abu-2 | - | - |
| uncommon | Sar-3 | - | - |
| stereo | Ala-8 | - | D |

SEQ 1 XXXLVLAALL V

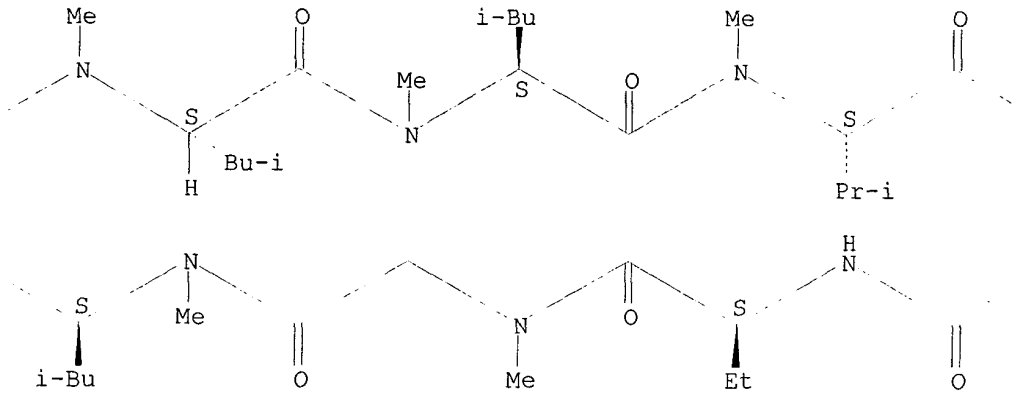
**RELATED SEQUENCES AVAILABLE WITH SEQLINK**
MF **C68 H116 N12 O16**
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.
Double bond geometry as shown.

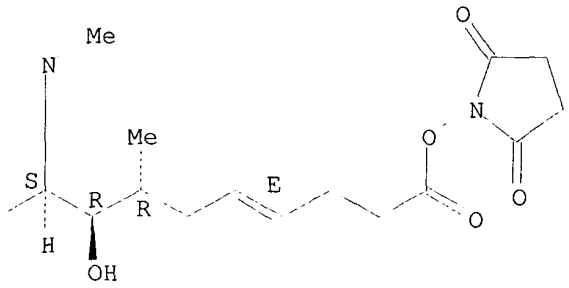
PAGE 1-A



PAGE 1-B



PAGE 1-C



1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:105954

L37 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2002 ACS
RN 219740-62-2 REGISTRY
CN Cyclo[L-alanyl-O-(2-hydroxyethyl)-D-seryl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl-(2S,3R,4R,6E)-7-carboxy-3-hydroxy-4-methyl-2-(methylamino)-6-heptenoyl-(2S)-2-aminobutanoyl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl] (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 11
NTE cyclic
modified (modifications unspecified)

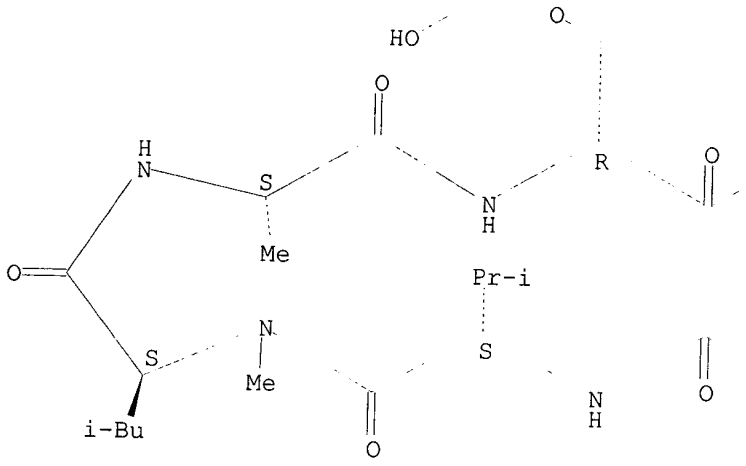
| type | ------ location ------ | | description |
|---|---|---|---|
| uncommon | Aaa-1 | - | - |
| uncommon | Abu-2 | - | - |
| uncommon | Sar-3 | - | - |

SEQ 1 XXXLVLASLL V

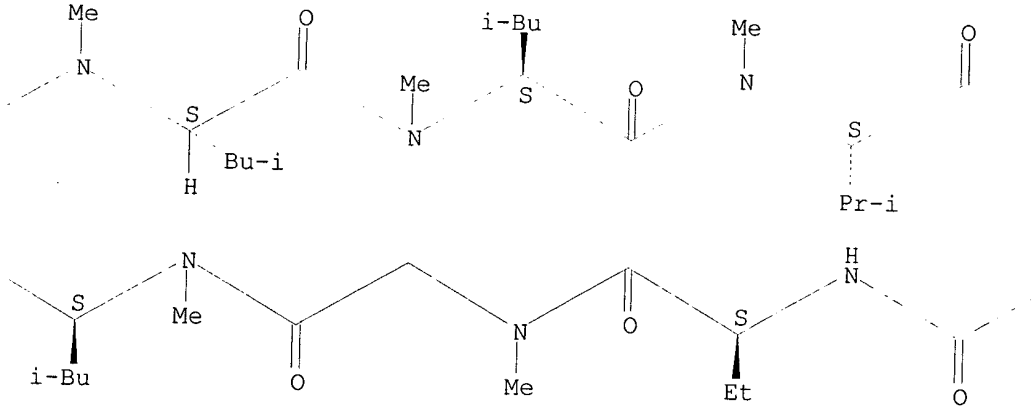
**RELATED SEQUENCES AVAILABLE WITH SEQLINK**
MF **C64 H113 N11 O16**
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.
Double bond geometry as shown.

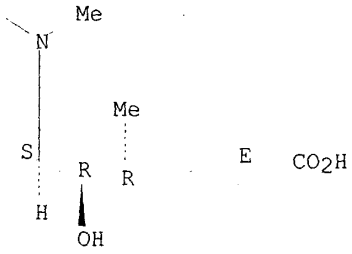
PAGE 1-A



PAGE 1-B



PAGE 1-C




1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 130:119267

L37 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2002 ACS
RN 177080-78-3 REGISTRY
CN Cyclosporin A, 6-[(3R,4R,6E)-9-carboxy-6,7-didehydro-3-hydroxy-N,4-dimethyl-L-2-aminononanoic acid]- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 11
NTE cyclic
modified (modifications unspecified)

| type | ------ location ------ | | description |
|---|---|---|---|
| uncommon | Aaa-1 | - | - |
| uncommon | Abu-2 | - | - |
| uncommon | Sar-3 | - | - |

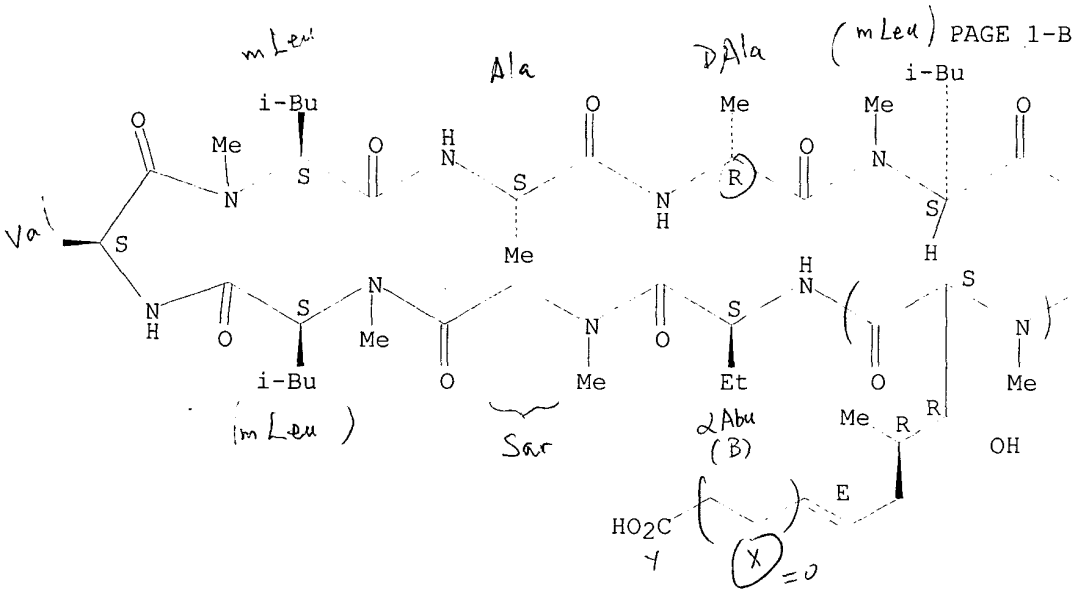
SEQ 1 XXXLVLAALL V

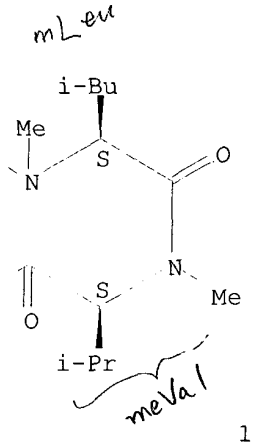
**RELATED SEQUENCES AVAILABLE WITH SEQLINK**
MF **C64 H113 N11 O14**
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A

i-Pr




1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 125:6043

=> d sqide can tot l8

L8 ANSWER 1 OF 17 REGISTRY COPYRIGHT 2002 ACS
RN **457613-11-5** REGISTRY
CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, anhydride with 9H-fluoren-9-ylmethyl hydrogen carbonate (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL **11**
NTE cyclic
modified (modifications unspecified)

| type | ------ location ------ | | description |
|---|---|---|---|
| uncommon | Aaa-1 | - | - |

| | | | |
|---|---|---|---|
| uncommon | Abu-2 | - | - |
| uncommon | Sar-3 | - | - |
| stereo | Ala-8 | - | D |

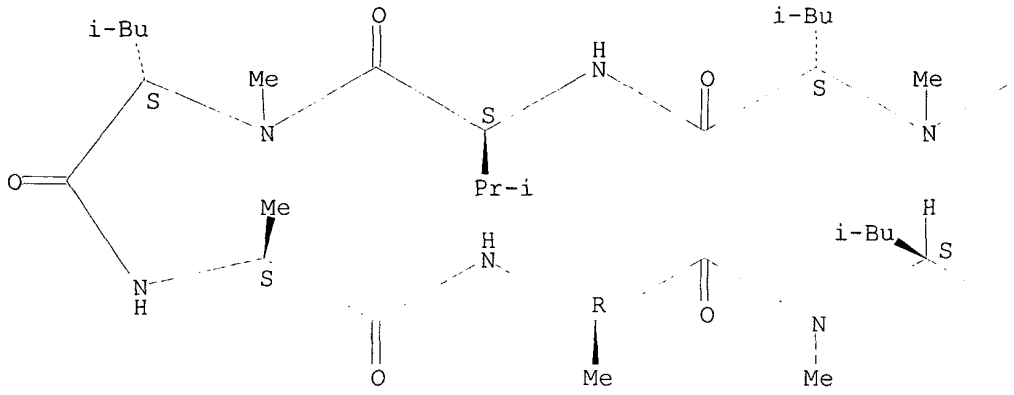
---

SEQ 1 XXXLVLAALL V

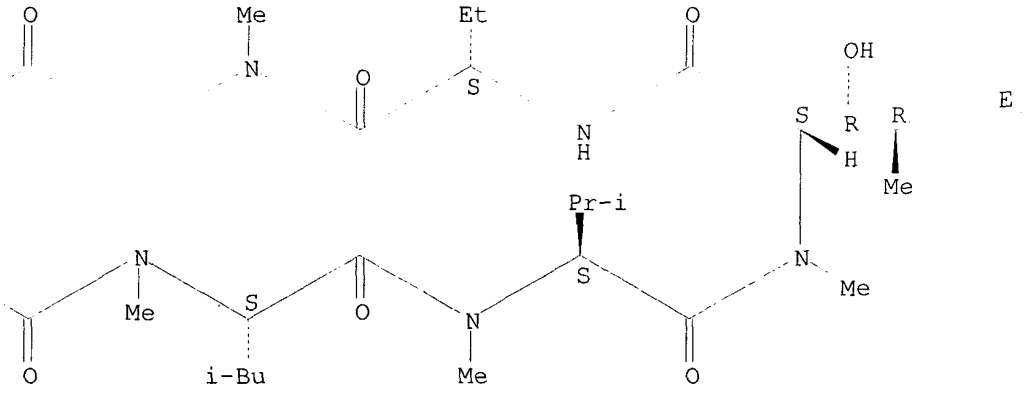
**RELATED SEQUENCES AVAILABLE WITH SEQLINK**
MF C77 H119 N11 O16
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.

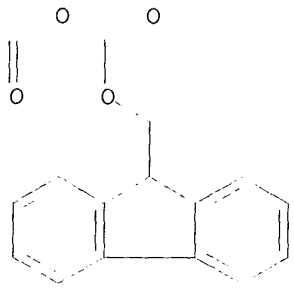
PAGE 1-A




PAGE 1-B



PAGE 1-C



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:226601

L8 ANSWER 2 OF 17 REGISTRY COPYRIGHT 2002 ACS
RN **457613-10-4** REGISTRY
CN Cyclosporin A, 6-[(5E,8R,9R,10S)-9-hydroxy-8-methyl-10-(methylamino)-5-undecenedioic acid]-, methyl ester (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL **11**
NTE cyclic
modified (modifications unspecified)

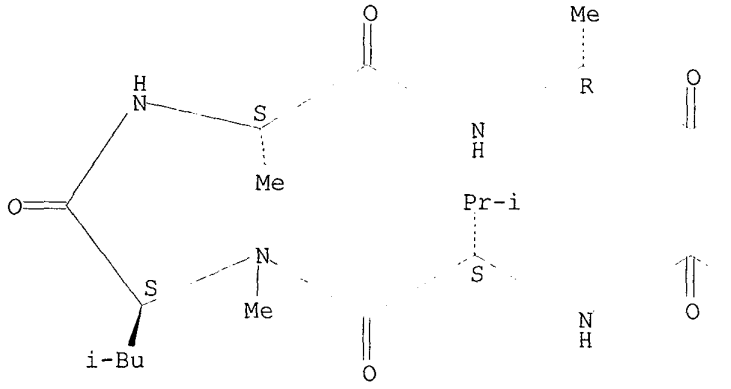
| type | ------ location ------ | | description |
|---|---|---|---|
| uncommon | Aaa-1 | - | - |
| uncommon | Abu-2 | - | - |
| uncommon | Sar-3 | - | - |
| stereo | Ala-8 | - | D |

SEQ 1 XXXLVLAALL V

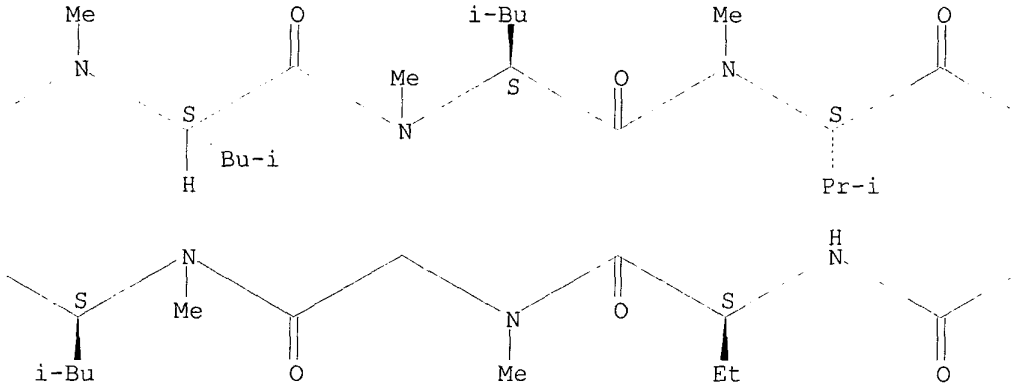
**RELATED SEQUENCES AVAILABLE WITH SEQLINK**
MF C66 H117 N11 O14
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.

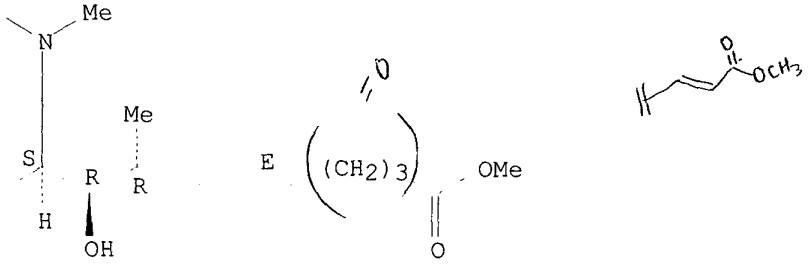
PAGE 1-A



PAGE 1-B



PAGE 1-C



1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:226601

L8 ANSWER 3 OF 17 REGISTRY COPYRIGHT 2002 ACS
RN **457613-09-1** REGISTRY
CN Cyclosporin A, 6-[(2S,3R,4R,6E)-3-hydroxy-4-methyl-2-(methylamino)-8-oxo-8-[(phenylmethyl)thio]-6-octenoic acid]- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL **11**
NTE cyclic
modified (modifications unspecified)

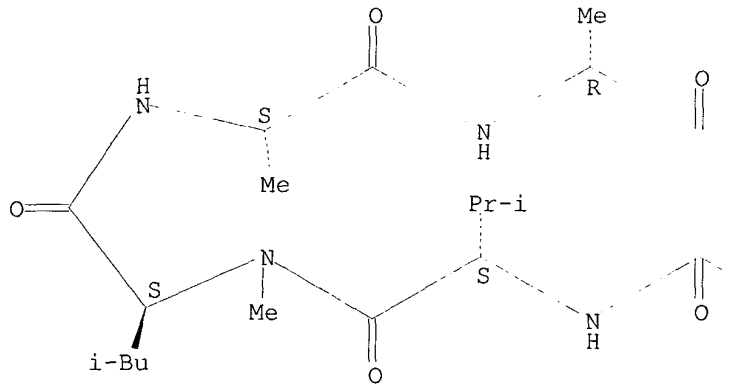
| type | location | | description |
|---|---|---|---|
| uncommon | Aaa-1 | - | - |
| uncommon | Abu-2 | - | - |
| uncommon | Sar-3 | - | - |
| stereo | Ala-8 | - | D |

SEQ 1 XXXLVLAALL V

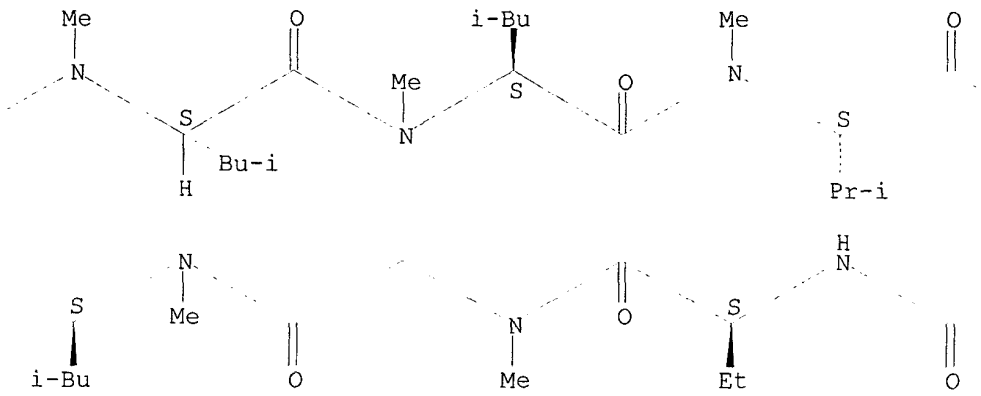
**RELATED SEQUENCES AVAILABLE WITH SEQLINK**
MF C69 H115 N11 O13 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.

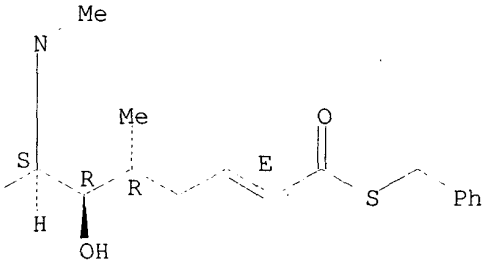
PAGE 1-A



PAGE 1-B



PAGE 1-C



1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:226601

L8 ANSWER 4 OF 17 REGISTRY COPYRIGHT 2002 ACS
RN **457613-08-0** REGISTRY
CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, (2-methoxyethoxy)methyl ester (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL **11**
NTE cyclic
modified (modifications unspecified)

| type | ------ location ------ | | description |
|---|---|---|---|
| uncommon | Aaa-1 | - | - |
| uncommon | Abu-2 | - | - |
| uncommon | Sar-3 | - | - |
| stereo | Ala-8 | - | D |

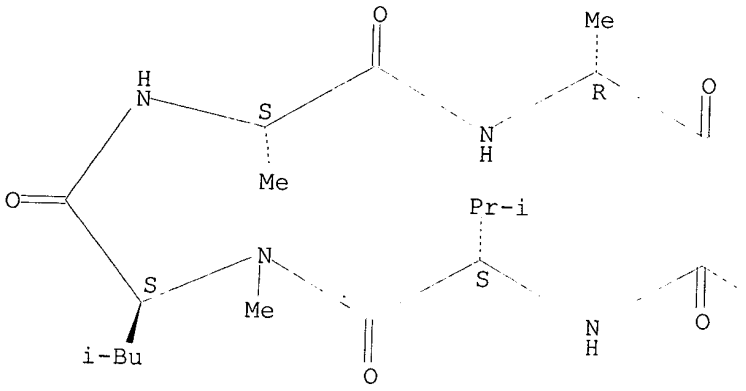
SEQ 1 XXXLVLAALL V

**RELATED SEQUENCES AVAILABLE WITH SEQLINK**

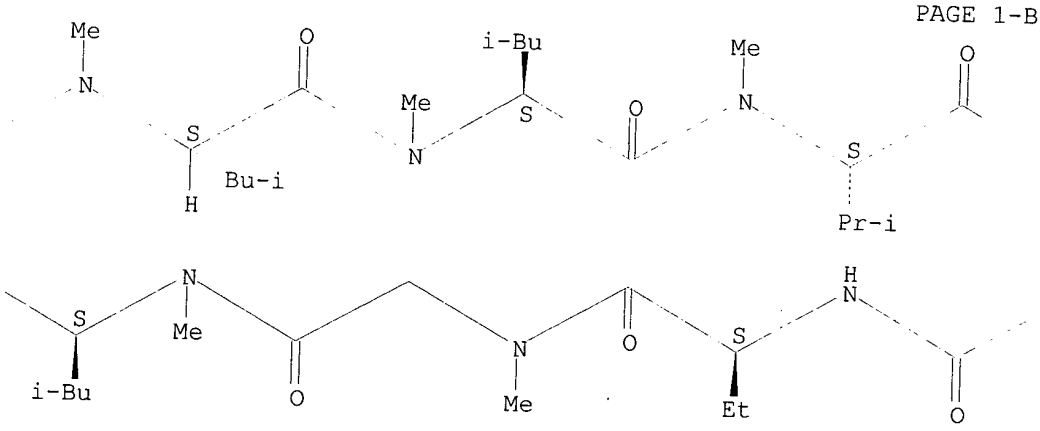
MF C66 H117 N11 O16
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.

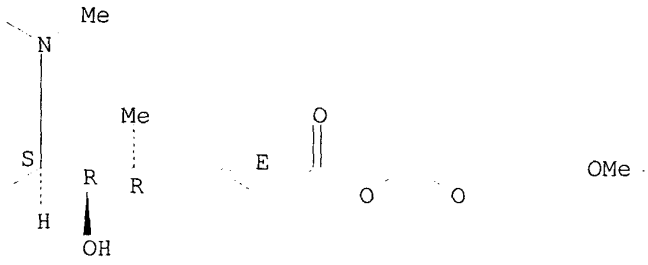
PAGE 1-A



PAGE 1-B



PAGE 1-C




1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:226601

L8 ANSWER 5 OF 17 REGISTRY COPYRIGHT 2002 ACS
RN **457613-07-9** REGISTRY
CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, methoxymethyl ester (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL **11**
NTE cyclic
modified (modifications unspecified)

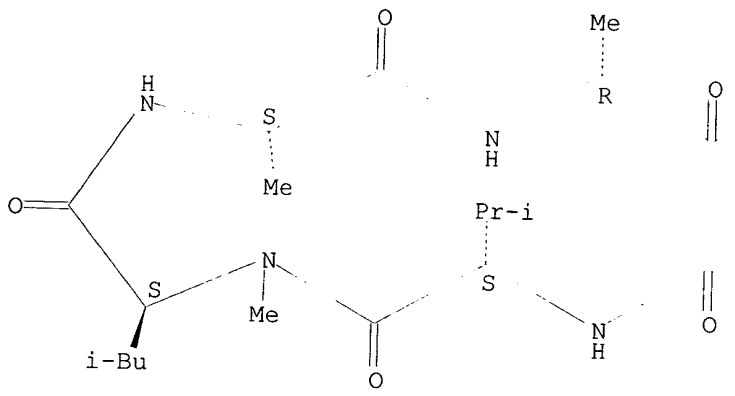
| type | ------ location ------ | | description |
|---|---|---|---|
| uncommon | Aaa-1 | - | - |
| uncommon | Abu-2 | - | - |
| uncommon | Sar-3 | - | - |
| stereo | Ala-8 | - | D |

SEQ 1 XXXLVLAALL V

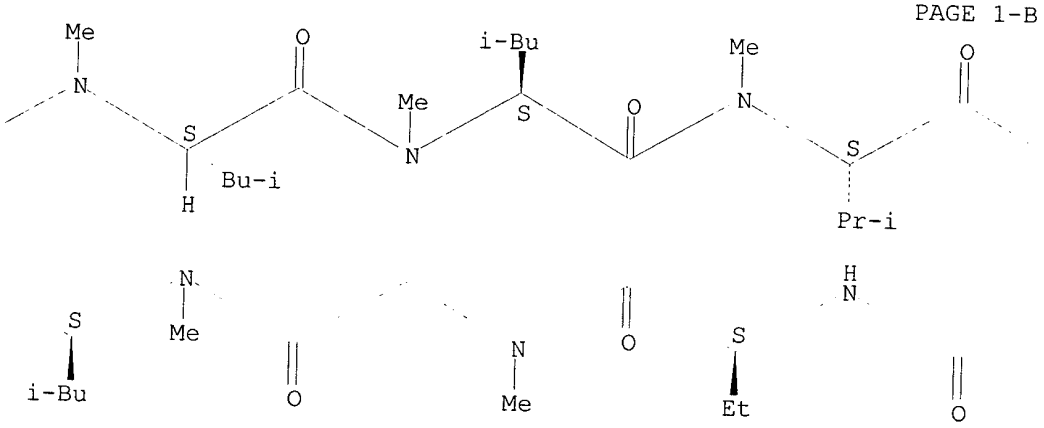
**RELATED SEQUENCES AVAILABLE WITH SEQLINK**
MF C64 H113 N11 O15
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.

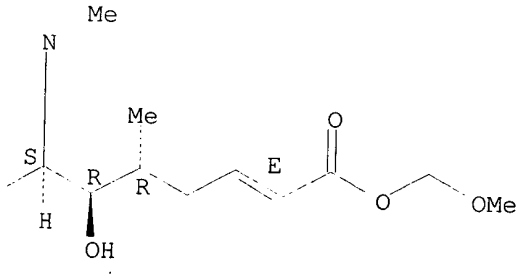
PAGE 1-A



PAGE 1-B



PAGE 1-C



1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:226601

L8 ANSWER 6 OF 17 REGISTRY COPYRIGHT 2002 ACS
RN **457613-06-8** REGISTRY
CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, chloromethyl ester (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL **11**
NTE cyclic
modified (modifications unspecified)

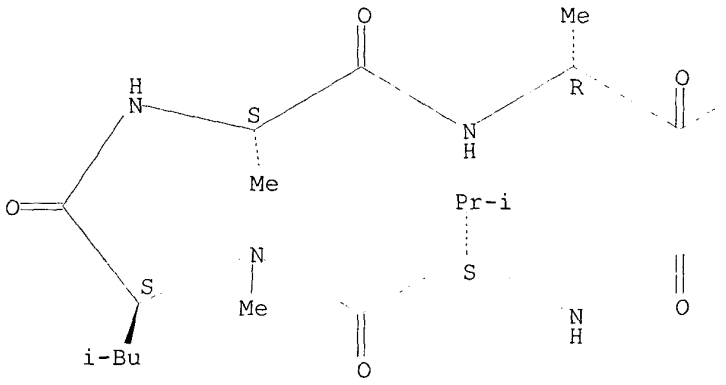
| type | ------ location ------ | | description |
|---|---|---|---|
| uncommon | Aaa-1 | - | - |
| uncommon | Abu-2 | - | - |
| uncommon | Sar-3 | - | - |
| stereo | Ala-8 | - | D |

SEQ 1 XXXLVLAALL V

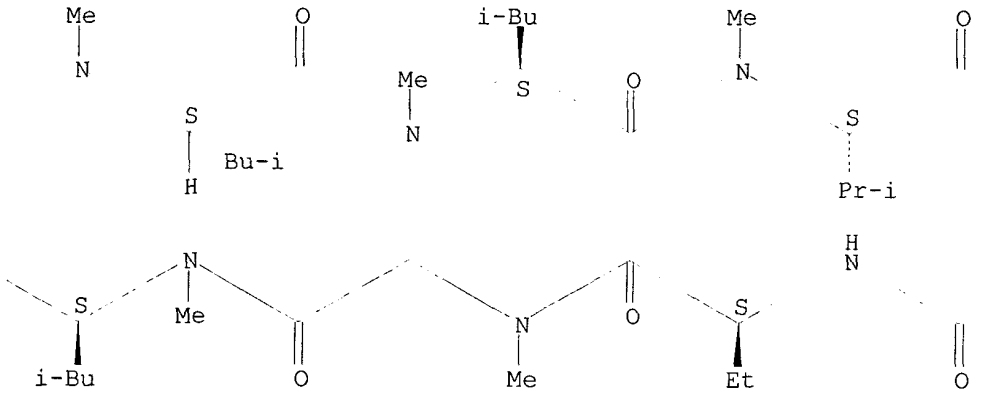
**RELATED SEQUENCES AVAILABLE WITH SEQLINK**
MF C63 H110 Cl N11 O14
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.

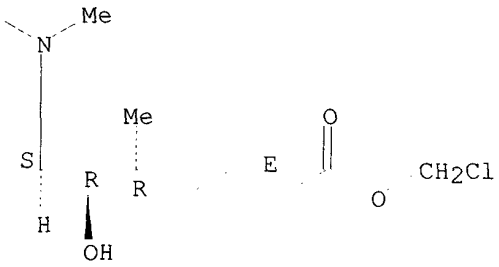
PAGE 1-A



PAGE 1-B



PAGE 1-C



1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:226601

L8 ANSWER 7 OF 17 REGISTRY COPYRIGHT 2002 ACS
RN **457613-05-7** REGISTRY
CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, 2,2,2-trifluoroethyl ester (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL **11**
NTE cyclic
modified (modifications unspecified)

| type | location | | description |
|---|---|---|---|
| uncommon | Aaa-1 | - | - |
| uncommon | Abu-2 | - | - |
| uncommon | Sar-3 | - | - |
| stereo | Ala-8 | - | D |

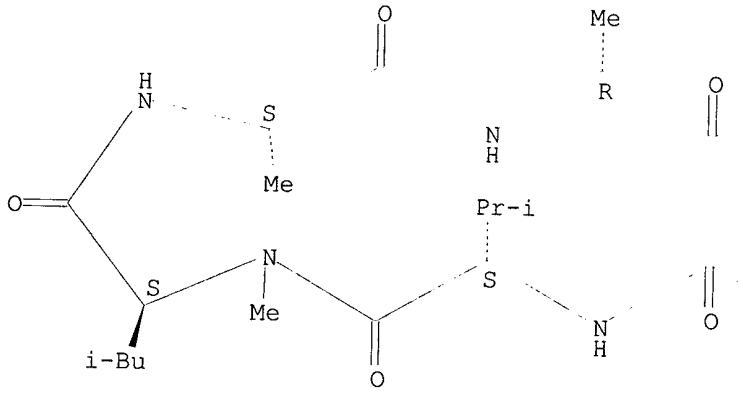
SEQ 1 XXXLVLAALL V

**RELATED SEQUENCES AVAILABLE WITH SEQLINK**

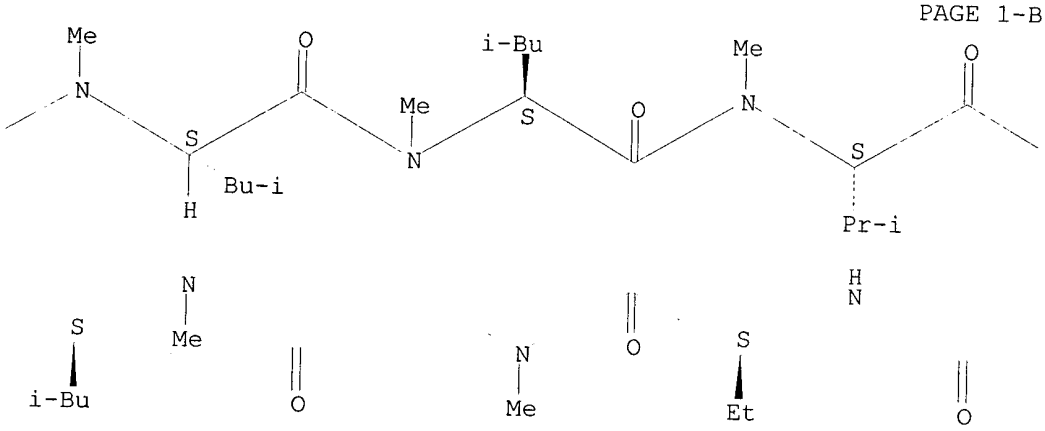
MF C64 H110 F3 N11 O14
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.

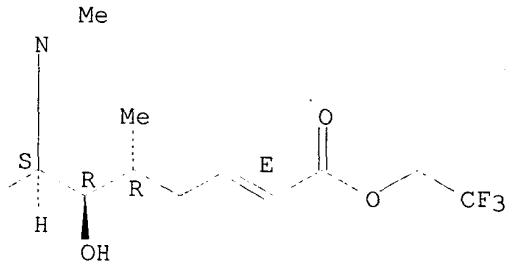
PAGE 1-A



PAGE 1-B



PAGE 1-C




1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:226601

L8 ANSWER 8 OF 17 REGISTRY COPYRIGHT 2002 ACS
RN **457613-04-6** REGISTRY
CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, trifluoromethyl ester (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL **11**
NTE cyclic
modified (modifications unspecified)

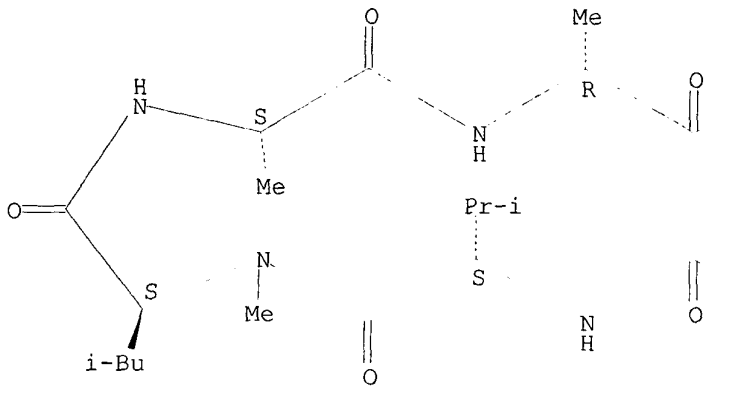
| type | ------ location ------ | | description |
|---|---|---|---|
| uncommon | Aaa-1 | - | - |
| uncommon | Abu-2 | - | - |
| uncommon | Sar-3 | - | - |
| stereo | Ala-8 | - | D |

SEQ 1 XXXLVLAALL V

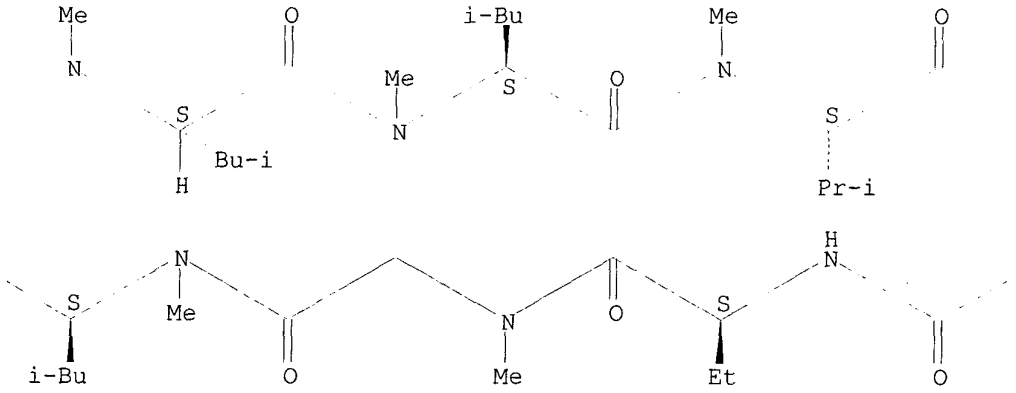
**RELATED SEQUENCES AVAILABLE WITH SEQLINK**
MF C63 H108 F3 N11 O14
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.

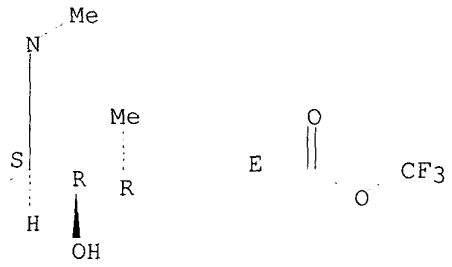
PAGE 1-A



PAGE 1-B



PAGE 1-C



1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:226601

L8 ANSWER 9 OF 17 REGISTRY COPYRIGHT 2002 ACS
RN **457613-03-5** REGISTRY
CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, difluoromethyl ester (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL **11**
NTE cyclic
modified (modifications unspecified)

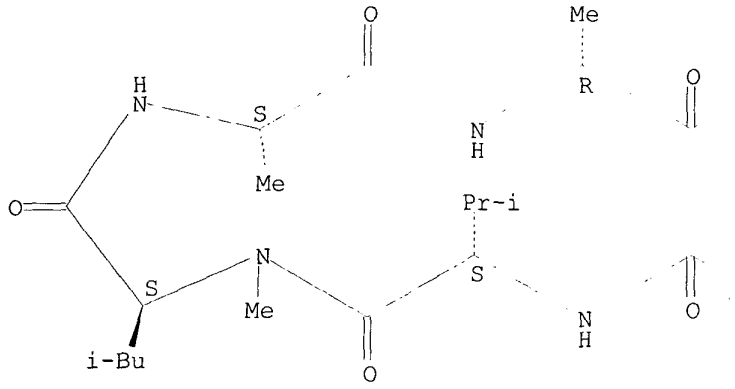
| type | ------ location ------ | | description |
|---|---|---|---|
| uncommon | Aaa-1 | - | - |
| uncommon | Abu-2 | - | - |
| uncommon | Sar-3 | - | - |
| stereo | Ala-8 | - | D |

SEQ 1 XXXLVLAALL V

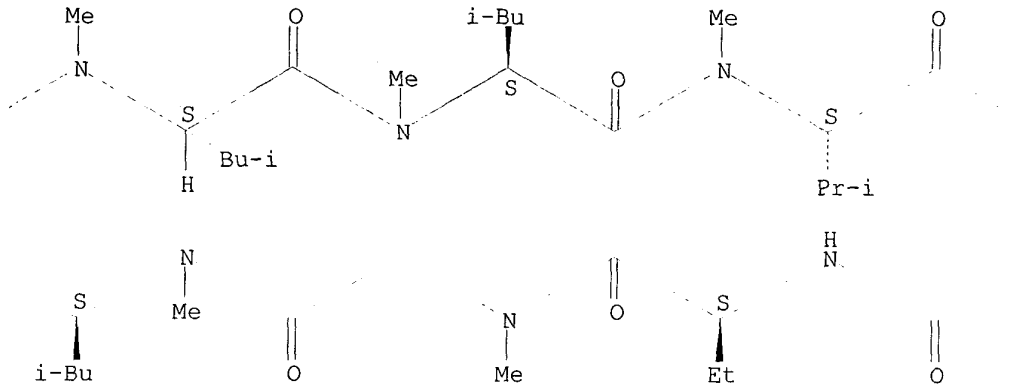
**RELATED SEQUENCES AVAILABLE WITH SEQLINK**
MF C63 H109 F2 N11 O14
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.

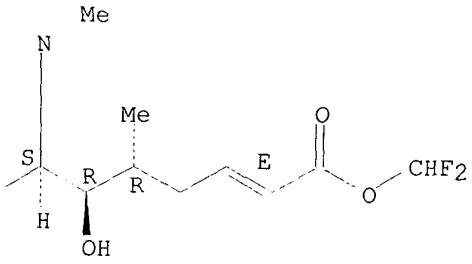
PAGE 1-A



PAGE 1-B



PAGE 1-C



1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:226601

L8 ANSWER 10 OF 17 REGISTRY COPYRIGHT 2002 ACS
RN **457613-02-4** REGISTRY
CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, fluoromethyl ester (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL **11**
NTE cyclic
modified (modifications unspecified)

| type | ------ location ------ | | description |
|---|---|---|---|
| uncommon | Aaa-1 | - | - |
| uncommon | Abu-2 | - | - |
| uncommon | Sar-3 | - | - |
| stereo | Ala-8 | - | D |

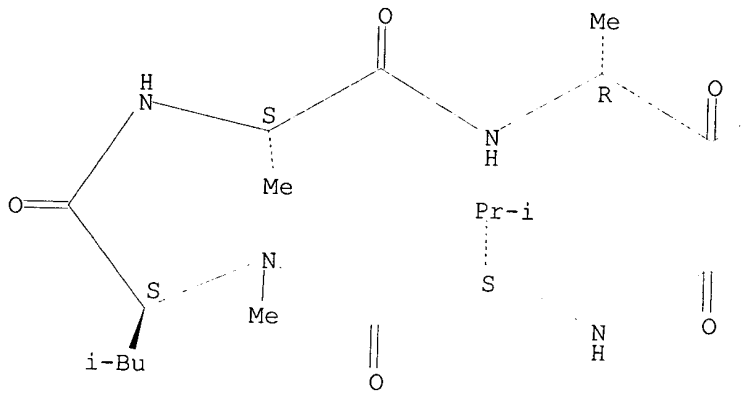
SEQ 1 XXXLVLAALL V

**RELATED SEQUENCES AVAILABLE WITH SEQLINK**

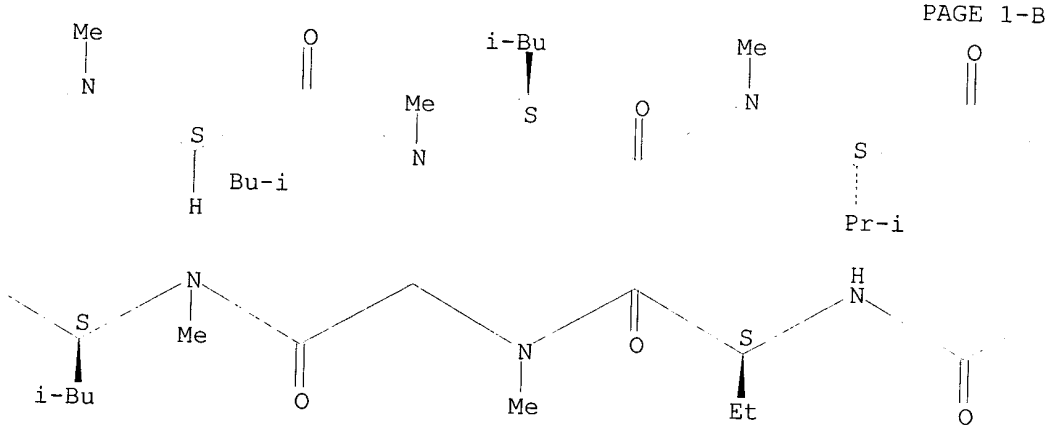
MF C63 H110 F N11 O14
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.

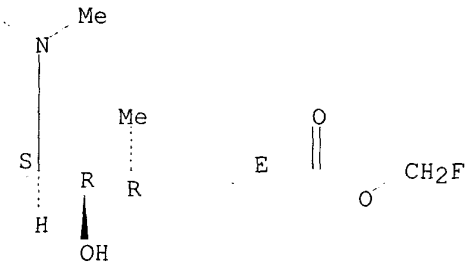
PAGE 1-A




PAGE 1-B



PAGE 1-C



1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:226601

L8 ANSWER 11 OF 17 REGISTRY COPYRIGHT 2002 ACS
RN **457613-01-3** REGISTRY
CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, phenylmethyl ester (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL **11**
NTE cyclic
modified (modifications unspecified)

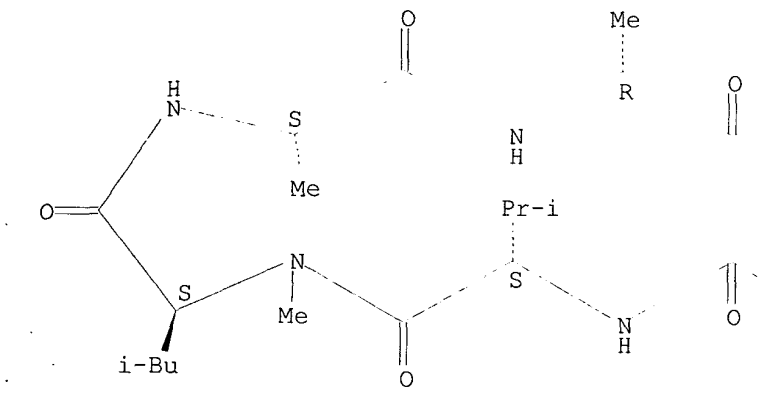
| type | ------ location ------ | | description |
|---|---|---|---|
| uncommon | Aaa-1 | - | - |
| uncommon | Abu-2 | - | - |
| uncommon | Sar-3 | - | - |
| stereo | Ala-8 | - | D |

SEQ 1 XXXLVLAALL V

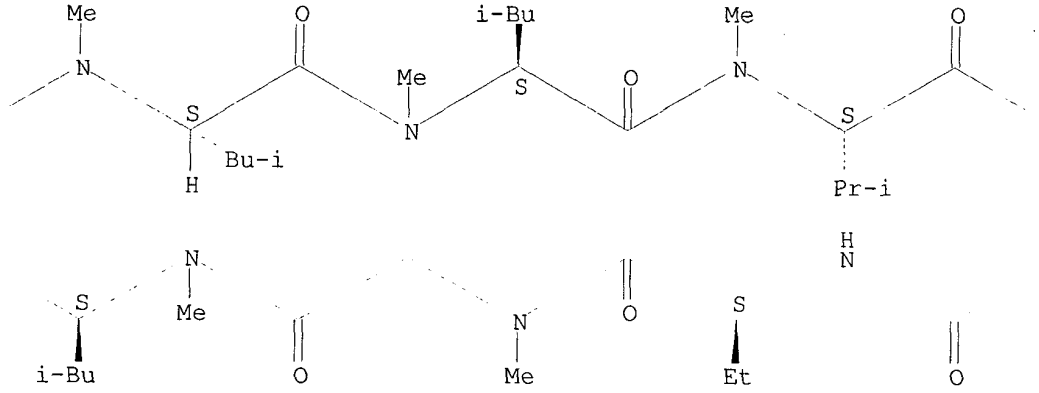
**RELATED SEQUENCES AVAILABLE WITH SEQLINK**
MF C69 H115 N11 O14
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.

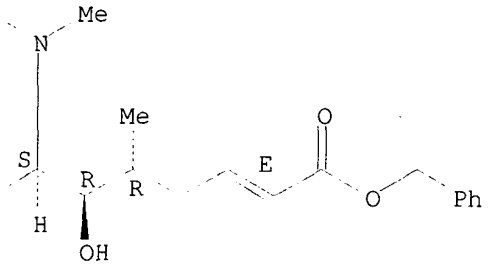
PAGE 1-A



PAGE 1-B



PAGE 1-C



1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:226601

L8 ANSWER 12 OF 17 REGISTRY COPYRIGHT 2002 ACS
RN **457613-00-2** REGISTRY
CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, propyl ester (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL **11**
NTE cyclic
modified (modifications unspecified)

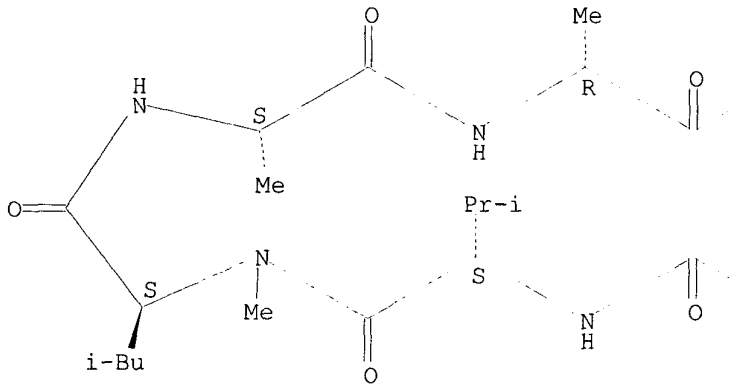
| type | ------ location ------ | | description |
|---|---|---|---|
| uncommon | Aaa-1 | - | - |
| uncommon | Abu-2 | - | - |
| uncommon | Sar-3 | - | - |
| stereo | Ala-8 | - | D |

SEQ 1 XXXLVLAALL V

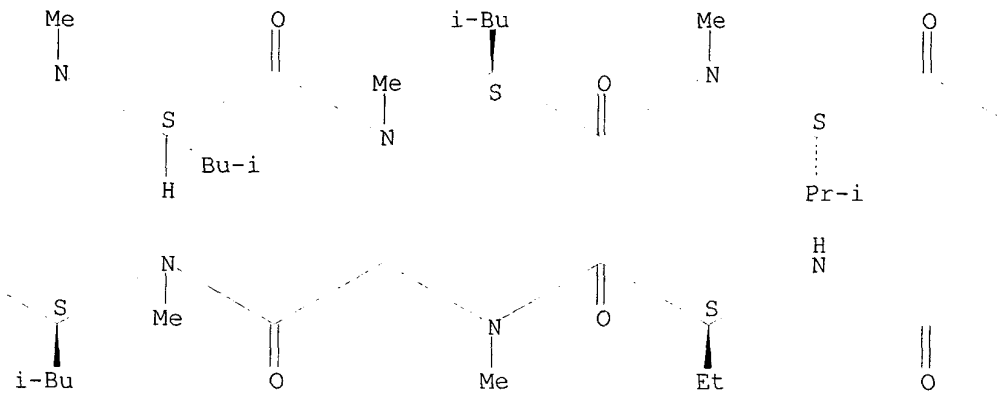
**RELATED SEQUENCES AVAILABLE WITH SEQLINK**
MF C65 H115 N11 O14
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.

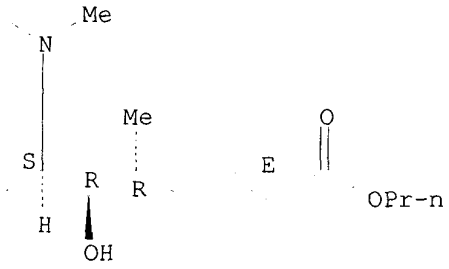
PAGE 1-A



PAGE 1-B



PAGE 1-C



1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:226601

L8 ANSWER 13 OF 17 REGISTRY COPYRIGHT 2002 ACS
RN **457612-99-6** REGISTRY
CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, butyl ester (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL **11**
NTE cyclic
modified (modifications unspecified)

| type | ------ location ------ | | description |
|---|---|---|---|
| uncommon | Aaa-1 | - | - |
| uncommon | Abu-2 | - | - |
| uncommon | Sar-3 | - | - |
| stereo | Ala-8 | - | D |

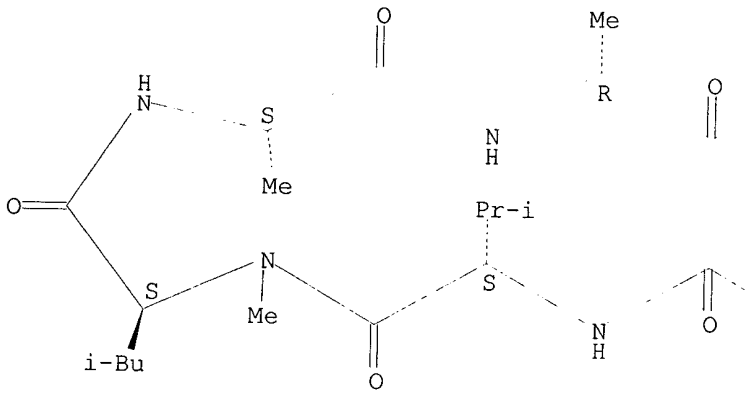
SEQ 1 XXXLVLAALL V

**RELATED SEQUENCES AVAILABLE WITH SEQLINK**

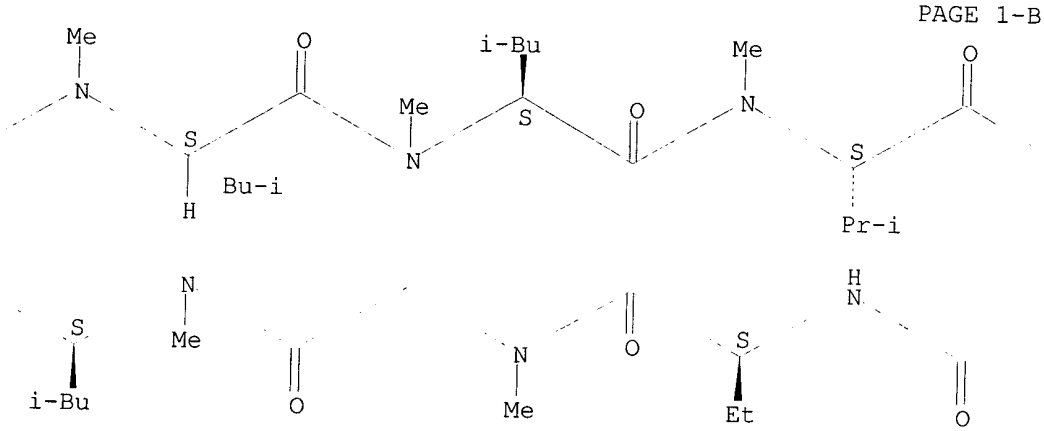
MF C66 H117 N11 O14
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.

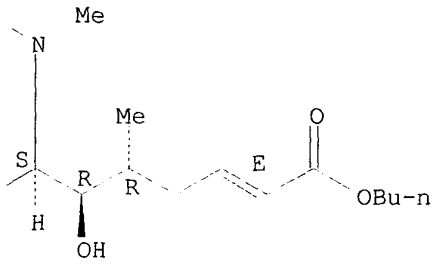
PAGE 1-A




PAGE 1-B



PAGE 1-C




1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:226601

L8 ANSWER 14 OF 17 REGISTRY COPYRIGHT 2002 ACS
RN **457612-98-5** REGISTRY
CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, ethyl ester (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL **11**
NTE cyclic
modified (modifications unspecified)

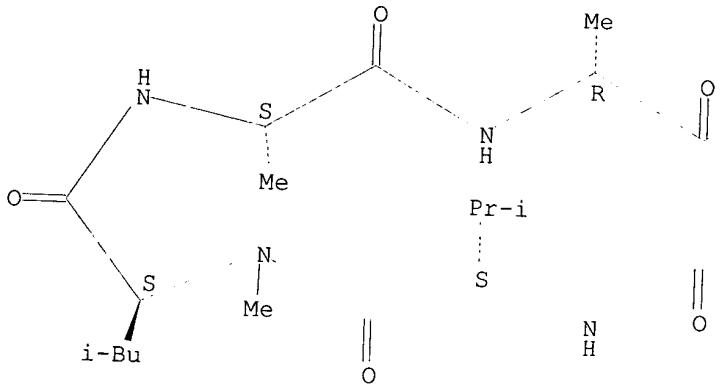
| type | location | | description |
|---|---|---|---|
| uncommon | Aaa-1 | - | - |
| uncommon | Abu-2 | - | - |
| uncommon | Sar-3 | - | - |
| stereo | Ala-8 | - | D |

SEQ 1 XXXLVLAALL V

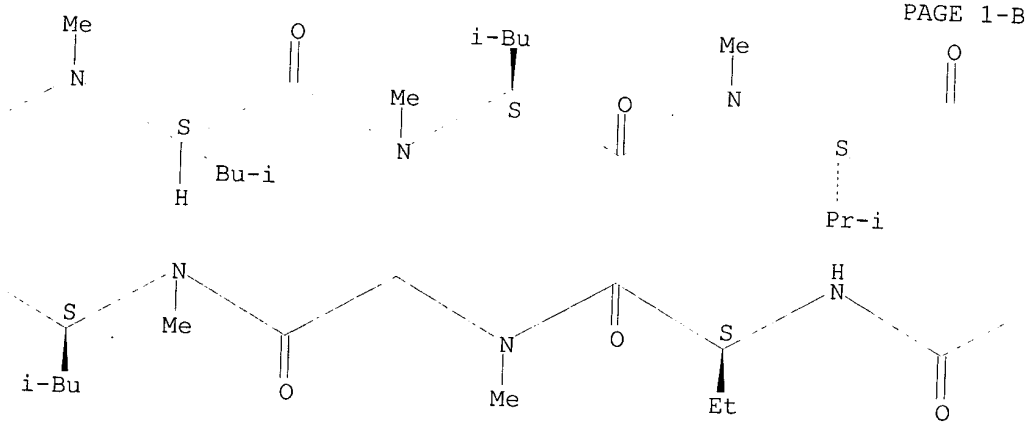
**RELATED SEQUENCES AVAILABLE WITH SEQLINK**
MF C64 H113 N11 O14
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.

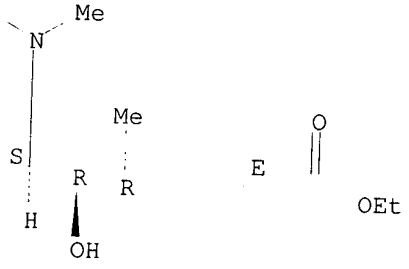
PAGE 1-A



PAGE 1-B



PAGE 1-C



1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:226601

L8 ANSWER 15 OF 17 REGISTRY COPYRIGHT 2002 ACS
RN **122547-85-7** REGISTRY
CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, methyl ester (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,4,7,10,13,16,19,22,25,28,31-Undecaazacyclotritriacontane, cyclic peptide deriv.
CN Cyclosporin A, 6-[(3R,4R)-6,7-didehydro-3-hydroxy-8-methoxy-N,4-dimethyl-8-oxo-L-2-aminooctanoic acid]-
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL **11**
NTE cyclic
modified (modifications unspecified)

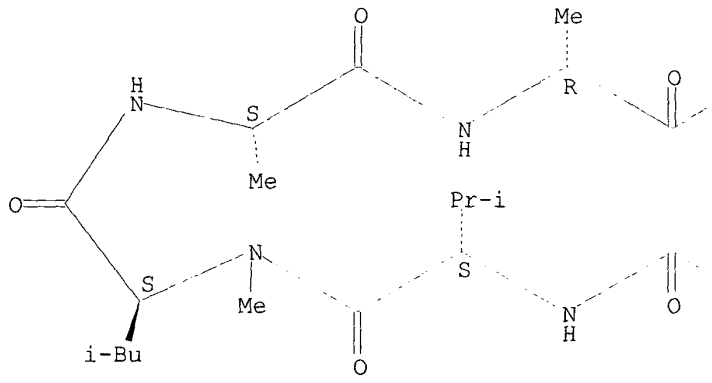
| type | ------ location ------ | | description |
|---|---|---|---|
| uncommon | Aaa-1 | - | - |
| uncommon | Abu-2 | - | - |
| uncommon | Sar-3 | - | - |
| stereo | Ala-8 | - | D |

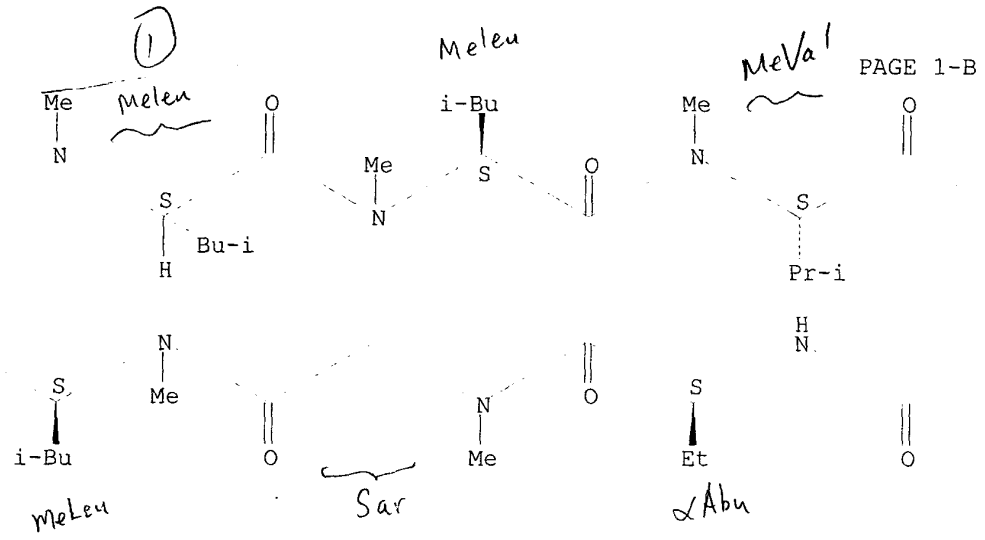
SEQ 1 XXXLVLAALL V

**RELATED SEQUENCES AVAILABLE WITH SEQLINK**
MF C63 H111 N11 O14
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

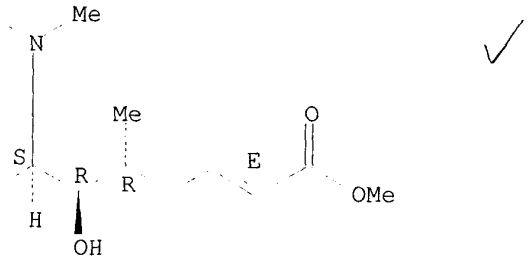
Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A






PAGE 1-C



2 REFERENCES IN FILE CA (1962 TO DATE)
2 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:226601

REFERENCE 2: 111:127017

---

L8 ANSWER 16 OF 17 REGISTRY COPYRIGHT 2002 ACS
RN **100364-58-7** REGISTRY
CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,4,7,10,13,16,19,22,25,28,31-Undecaazacyclotritriacontane, cyclic peptide deriv.
CN Cyclosporin A, 6-[(3R,4R,6E)-6,7-didehydro-3-hydroxy-N,4-dimethyl-L-2-aminooctanedioic acid]-
OTHER NAMES:
CN AM 1A
CN Cyclosporin A metabolite 203-218
CN M 203-218
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL **11**
NTE cyclic
modified (modifications unspecified)
---

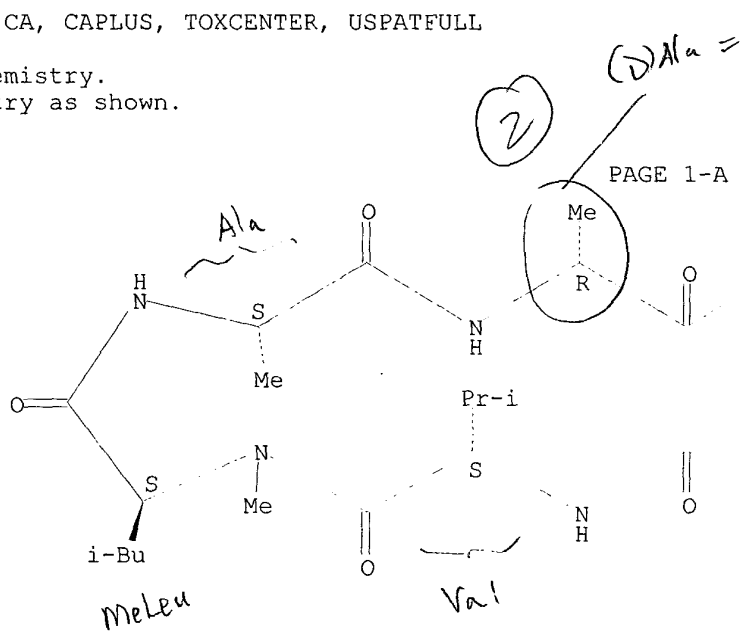
| type | ------ location ------ | | description |
|---|---|---|---|
| uncommon | Aaa-1 | - | - |
| uncommon | Abu-2 | - | - |
| uncommon | Sar-3 | - | - |
| stereo | Ala-8 | - | D |

SEQ 1 XXXLVLAALL V

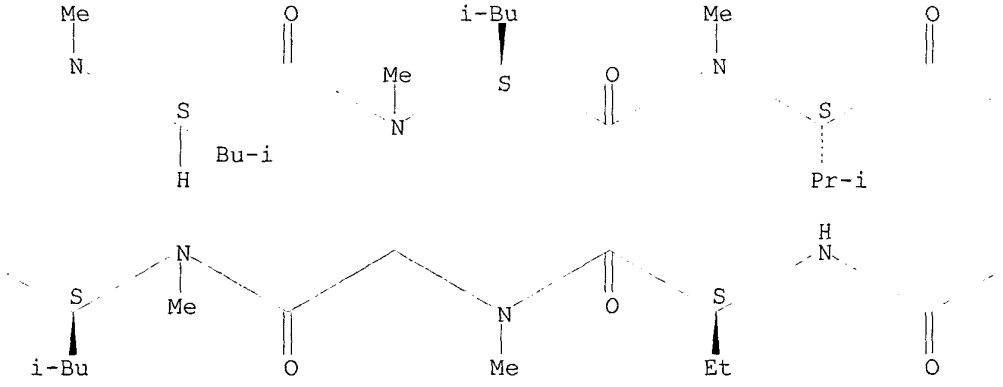
**RELATED SEQUENCES AVAILABLE WITH SEQLINK**
DR 122547-86-8
MF C62 H109 N11 O14
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.

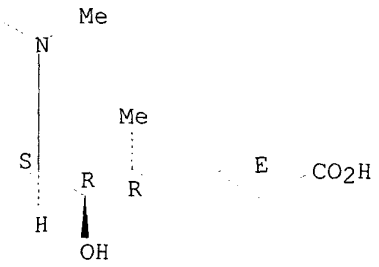
PAGE 1-A




PAGE 1-B



PAGE 1-C




25 REFERENCES IN FILE CA (1962 TO DATE)
25 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:226601

REFERENCE 2: 135:86519

REFERENCE 3: 124:306383

REFERENCE 4: 117:83083

REFERENCE 5: 116:15264

REFERENCE 6: 115:270244

REFERENCE 7: 115:269869

REFERENCE 8: 115:149642

REFERENCE 9: 115:105665

REFERENCE 10: 115:64248

L8 ANSWER 17 OF 17 REGISTRY COPYRIGHT 2002 ACS
RN **59865-13-3** REGISTRY
CN Cyclosporin A (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,4,7,10,13,16,19,22,25,28,31-Undecaazacyclotritriacontane, cyclic peptide deriv.
OTHER NAMES:
CN 7: PN: WO0002548 PAGE: 30 claimed protein
CN Antibiotic S 7481F1
CN Ciclosporin
CN Cipol N
CN Consupren
CN Cyclosporin
CN Cyclosporine
CN Cyclosporine A
CN Cyclo[L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl-(3R,4R,6E)-6,7-didehydro-3-hydroxy-N,4-dimethyl-L-2-aminooctanoyl-L-2-aminobutanoyl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl]
CN Neoplanta
CN Neoral
CN OL 27-400
CN Ramihyphin A

CN S-Neoral
CN Sandimmun
CN Sandimmun Neoral
CN Sandimmune
CN Sang-35
CN SangCyA
CN SDZ-OXL 400
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL **11**
NTE cyclic
modified (modifications unspecified)

| type | ------ location ------ | | description |
|---|---|---|---|
| uncommon | Aaa-1 | - | - |
| uncommon | Abu-2 | - | - |
| uncommon | Sar-3 | - | - |
| stereo | Ala-8 | - | D |

PATENT ANNOTATIONS (PNTE):

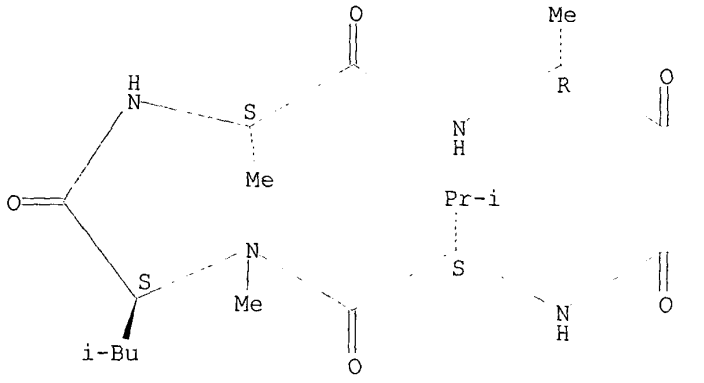
| Sequence Source | Patent Reference |
|---|---|
| Not Given | WO2000002548 claimed PAGE 30 |

SEQ 1 XXXLVLAALL V

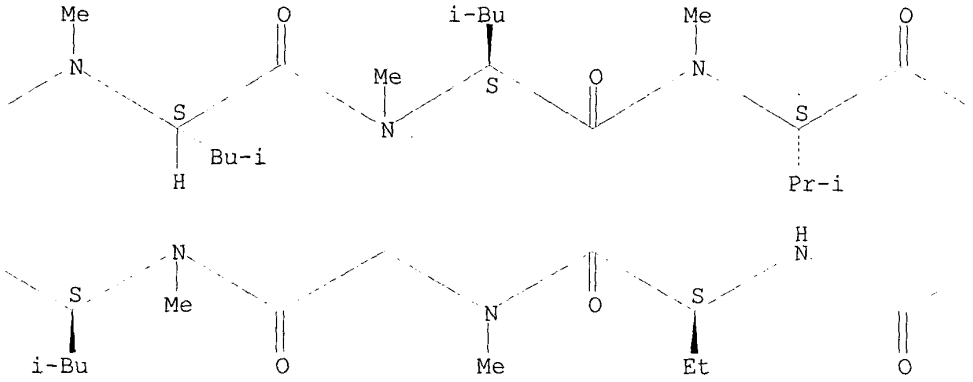
**RELATED SEQUENCES AVAILABLE WITH SEQLINK**
DR 56645-58-0, 55126-45-9, 104250-72-8, 223528-56-1
MF C62 H111 N11 O12
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PHAR, PHARMASEARCH, PROMT, RTECS*, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: WHO

Absolute stereochemistry.
Double bond geometry as shown.

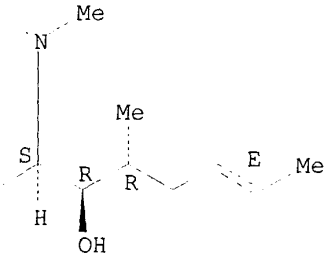
PAGE 1-A



PAGE 1-B



PAGE 1-C



11693 REFERENCES IN FILE CA (1962 TO DATE)
297 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
11721 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:358273

REFERENCE 2: 137:358158

REFERENCE 3: 137:357970

REFERENCE 4: 137:352901

REFERENCE 5: 137:351400

REFERENCE 6: 137:351382

REFERENCE 7: 137:351341

REFERENCE 8: 137:351074

REFERENCE 9: 137:349850

REFERENCE 10: 137:348601

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 15:34:49 ON 12 DEC 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.


FILE COVERS 1907 - 12 Dec 2002 VOL 137 ISS 24
FILE LAST UPDATED: 11 Dec 2002 (20021211/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

=> d all tot l44

L44 ANSWER 1 OF 29 HCAPLUS COPYRIGHT 2002 ACS
AN 2002:695724 HCAPLUS
DN 137:226601
TI Cyclosporins for the treatment of respiratory diseases
IN **Or, Yat Sun; Lazarova, Tsvetelina**; Hamann, Blake Christopher
PA **Enanta Pharmaceuticals, Inc., USA**
SO PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K

CC 1-7 (Pharmacology)
Section cross-reference(s): 34, 63
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 2002069902 | A2 | 20020912 | WO 2002-US6541 | 20020305 <-- |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

| | | | | | |
|---|---|---|---|---|---|
| | US 2002142946 | A1 | 20021003 | US 2001-800856 | 20010305 <-- |
| PRAI | US 2001-800856 | A | 20010305 <-- | | |

OS MARPAT 137:226601

AB Novel semisynthetic cyclosporin analogs contg. different amino acids are synthesized for use as pharmaceuticals. The compds. can be used for th treatment of asthma, allergic rhinitis, bronchitis, etc. Thus, cyclosporin analogs were prepd. and their immunosuppressant activity was detd. by using the inhibition of the phosphate activity as the parameter.

ST cyclosporin analog topical respiratory disease prepn

IT Catalysts
(Nolan's; cyclosporins for the treatment of respiratory diseases)

IT Nose
(allergic rhinitis; cyclosporins for the treatment of respiratory diseases)

IT Bronchi
(bronchitis; cyclosporins for the treatment of respiratory diseases)

IT Bronchi
(chronic bronchitis; cyclosporins for the treatment of respiratory diseases)

IT Lung, disease
(chronic obstructive; cyclosporins for the treatment of respiratory diseases)

IT Anti-inflammatory agents
Asthma
Cystic fibrosis
Immunosuppressants
Lymphocyte
(cyclosporins for the treatment of respiratory diseases)

IT Respiratory tract
(disease; cyclosporins for the treatment of respiratory diseases)

IT Drug delivery systems
(inhalants; cyclosporins for the treatment of respiratory diseases)

IT Drug delivery systems
(topical; cyclosporins for the treatment of respiratory diseases)

IT 172222-30-9, Grubbs' ruthenium catalyst 223415-64-3
RL: CAT (Catalyst use); USES (Uses)
(cyclosporins for the treatment of respiratory diseases)

IT **100364-58-7P 457612-98-5P 457612-99-6P**
**457613-00-2P 457613-01-3P 457613-02-4P**
**457613-03-5P 457613-04-6P 457613-05-7P**
**457613-06-8P 457613-07-9P 457613-08-0P**
**457613-09-1P 457613-10-4P 457613-11-5P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cyclosporins for the treatment of respiratory diseases)

IT 96-33-3, Methyl acrylate 624-48-6, Methyl maleate
RL: RCT (Reactant); RACT (Reactant or reagent)

(cyclosporins for the treatment of respiratory diseases)
IT **122547-85-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(cyclosporins for the treatment of respiratory diseases)
IT 59865-13-3, Cyclosporin A
RL: RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(cyclosporins for the treatment of respiratory diseases)

L44 ANSWER 2 OF 29 HCAPLUS COPYRIGHT 2002 ACS
AN 2002:365395 HCAPLUS
DN 137:105954
TI Synthesis of Cyclosporin A-Derived Affinity Reagents by Olefin Metathesis
AU Smulik, Jason A.; Diver, Steven T.; Pan, Fan; Liu, Jun O.
CS Department of Chemistry, University at Buffalo the State University of New York, Amherst, NY, 14260, USA
SO Organic Letters (2002), 4(12), 2051-2054
CODEN: ORLEF7; ISSN: 1523-7060
PB American Chemical Society
DT Journal
LA English
CC 9-14 (Biochemical Methods)
Section cross-reference(s): 28
AB New affinity reagents were synthesized using alkene metathesis to directly modify the MeBmt side chain of cyclosporin A. The reagents were used to detect novel cyclophilins from cellular exts.
ST cyclosporin A affinity reagent prepn olefin metathesis
IT Alkenes, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metathesis; synthesis of cyclosporin A-derived affinity reagents by olefin metathesis)
IT Organic synthesis
(synthesis of cyclosporin A-derived affinity reagents by olefin metathesis)
IT Cyclophilins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(synthesis of cyclosporin A-derived affinity reagents by olefin metathesis)
IT 406502-99-6
RL: CAT (Catalyst use); USES (Uses)
(synthesis of cyclosporin A-derived affinity reagents by olefin metathesis)
IT 59865-13-3, Cyclosporin A
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis of cyclosporin A-derived affinity reagents by olefin metathesis)
IT **442912-25-6P** 442912-26-7P 442912-27-8P 442912-28-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of cyclosporin A-derived affinity reagents by olefin metathesis)
IT 9012-36-6P, Sepharose
RL: RGT (Reagent); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of cyclosporin A-derived affinity reagents by olefin metathesis)
RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Belshaw, P; Angew Chem, Int Edt Engl 1995, V34, P2129 HCAPLUS
(2) Belshaw, P; J Am Chem Soc 1997, V119, P1805 HCAPLUS
(3) Chatterjee, A; J Am Chem Soc 2000, V122, P3783 HCAPLUS
(4) Chatterjee, A; Org Lett 1999, V1, P1751 HCAPLUS

(5) Diver, S; J Am Chem Soc 1997, V119, P5106 HCAPLUS
(6) Fehr, T; J Antibiot 1999, V52, P474 HCAPLUS
(7) Fesik, S; Science 1990, V250, P1406 HCAPLUS
(8) Fischer, G; Nature 1989, V337, P476 HCAPLUS
(9) Harding, M; Science 1984, V226, P544
(10) Liu, J; Biochemistry 1992, V31, P3896 HCAPLUS
(11) Liu, J; Cell 1991, V66, P807 HCAPLUS
(12) Miller, S; J Am Chem Soc 1996, V118, P9606 HCAPLUS
(13) Park, S; Tetrahedron Lett 1989, V30, P4215 HCAPLUS
(14) Quesniaux, V; Eur J Immunol 1987, V17, P1359 HCAPLUS
(15) Sanford, M; J Am Chem Soc 2001, V123, P6543 HCAPLUS
(16) Sanford, M; J Am Chem Soc 2001, V123, P749 HCAPLUS
(17) Sanglier, J; J Antibiot 1999, V52, P466 HCAPLUS
(18) Scholl, M; Org Lett 1999, V1, P953 HCAPLUS
(19) Schreiber, S; Science 1991, V251, P283 HCAPLUS
(20) Spencer, D; Science 1993, V262, P1019 HCAPLUS
(21) Takahashi, N; Nature 1989, V337, P473 HCAPLUS
(22) Trnka, T; Acc Chem Res 2001, V34, P18 HCAPLUS
(23) Walsh, C; J Biol Chem 1992, V267, P13115 HCAPLUS

L44 ANSWER 3 OF 29 HCAPLUS COPYRIGHT 2002 ACS
AN 2001:262803 HCAPLUS
DN 135:86519
TI Cyclosporin A metabolism in brown bullhead, Ameriurus nebulosus
AU Jegorov, A.; Halada, P.; Safarcik, K.
CS Galena a.s., Ceske Budejovice, 370 05, Czech Rep.
SO Fish Physiology and Biochemistry (**2001**), Volume Date 2000, 23(3), 257-264
CODEN: FPBIEP; ISSN: 0920-1742
PB Kluwer Academic Publishers
DT Journal
LA English
CC 1-2 (Pharmacology)
Section cross-reference(s): 12
AB Fungi suggested to be used in the control of mosquito larvae produce biol. active cyclopeptides - cyclosporins, which can potentially accumulate in the fish feeding the infected larvae. Whereas toxicity of cyclosporins was obsd. at the higher doses in man and various exptl. animals, the fish tolerated surprisingly high cyclosporin blood levels. Hydroxycyclosporins predominated among metabolites excreted into water. In contrast, various N-demethylated cyclosporins created the major part of metabolites identified in the liver and bile. Two new metabolites are described - AM1N and AM6N,10N, which were not so far reported from mammals. Due to the much higher tolerance to cyclosporin, brown bullhead can serve the exptl. model to obtain cyclosporin metabolites.
ST bullhead Ameriurus cyclosporine metab
IT Ictalurus nebulosus
(cyclosporin A metab. in brown bullhead, Ameriurus nebulosus)
IT 59865-13-3, Cyclosporin A
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cyclosporin A metab. in brown bullhead, Ameriurus nebulosus)
IT 89270-23-5 89270-25-7 89270-26-8 89270-28-0 **100364-58-7** 348084-97-9 348085-00-7
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(cyclosporin A metab. in brown bullhead, Ameriurus nebulosus)
RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE

(1) Biemann, K; Mass Spectrom Rev 1987, V6, P1 HCAPLUS
(2) Bowers, L; Clin Chem 1990, V36, P1875 HCAPLUS
(3) Bowers, V; Transplantation 1991, V51, P847 MEDLINE
(4) Brooks, C; Clin Chem 1993, V39, P457 HCAPLUS

(5) Celander, M; Fish Physiol Biochem 1996, V15, P323 HCAPLUS
(6) Goksoyr, A; Aquatic Toxicol 1992, V22, P287
(7) Hartman, N; Biochem Biomed Res Commun 1985, V133, P964 HCAPLUS
(8) Hasspieler, B; Aquatic Toxicol 1994, V28, P53 HCAPLUS
(9) Havlicek, V; J Mass Spectrom 1995, V30, P940 HCAPLUS
(10) Havlicek, V; Org Mass Spectrom 1993, V28, P1440 HCAPLUS
(11) James, M; Drug Metabol Disp 1997, V25, P346 HCAPLUS
(12) Jegorov, A; Phytochemistry 1995, V38, P403 HCAPLUS
(13) Lee, S; Arch Biochem Biophys 1998, V360, P53 HCAPLUS
(14) Lensmeyer, G; Clin Chem 1987, V33, P1851 HCAPLUS
(15) Lorenz, W; Agents and Actions 1982, V12, P64 HCAPLUS
(16) Nassberger, L; Int J Exp Pathol 1991, V72, P365 MEDLINE
(17) Perkins, E; Comp Biochem Physiol C Pharmacol Toxicol Endocrinol 1998, V121, P305 MEDLINE
(18) Pichard, L; Biochem Pharmacol 1996, V51, P591 HCAPLUS
(19) Podsiadlowski, L; Comparativ Biochem Physiol B 1998, V121, P443 MEDLINE
(20) Prueksaritanont, T; Drug Metabol Disp 1993, V21, P730 HCAPLUS
(21) Sedmera, P; Tetrahedron Lett 1995, V36, P6953 HCAPLUS
(22) Soares, G; J Invertebr Pathol 1985, V46, P115
(23) Stegeman, J; Marine Environ Res 1992, V34, P133 HCAPLUS
(24) Tomolang, M; Pharmacol Res 1995, V32, P141
(25) Traber, R; Helv Chim Acta 1986, V70, P13
(26) Venkataramanan, R; Transplant Proc 1988, V20, P680 HCAPLUS
(27) Weiser, J; Folia Parasitol 1991, V38, P363 MEDLINE
(28) Wenger, R; Progr Chem Org Nat Products 1986, V50, P123 HCAPLUS
(29) Whalen, R; Xenobiotica 1999, V29, P3 HCAPLUS

L44 ANSWER 4 OF 29 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:743427 HCAPLUS
DN 130:119267
TI Isolation, identification and immunosuppressive activity of a new IMM-125 metabolite from human liver microsomes. Identification of its cyclophilin A-IMM-125 metabolite complex by nanospray tandem mass spectrometry
AU Lhoest, G. J. J.; De Jong, A. P. J. M.; Meiring, H. D.; Maton, N.; Latinne, D.; Verbeeck, R. K.; Otte, J. B.; Zurini, M.
CS Department of Pharmaceutical Sciences-UCL, Pharmacokinetics and Metabolism Unit, FATC Laboratory of Mass Spectrometry, Brussels, B-1200, Belg.
SO Journal of Mass Spectrometry (**1998**), 33(10), 936-942
CODEN: JMSPFJ; ISSN: 1076-5174
PB John Wiley & Sons Ltd.
DT Journal
LA English
CC 1-7 (Pharmacology)
AB The isolation from human liver microsomes and identification by electrospray mass spectrometry and tandem mass spectrometry of a new metabolite of IMM-125 resulting from the biotransformation of the amino acid 1 vinylic Me group to a carboxylic acid, called the IMM-125-COOH metabolite, is described. It was found that the complex of this new metabolite with cyclophilin A is formed less easily than the corresponding cyclophilin A-IMM-125-CH2OH main metabolite and cyclophilin A-IMM-125 complexes. However, when formed, the IMM-125-COOH metabolite-cyclophilin A complex requires more collision-induced dissocn. (CID) to dissoc. the complex than the complexes formed with the two other ligands. The nanospray tandem mass spectrum of the IMM-125-COOH metabolite-cyclophilin A complex (m/z 1755) gives rise to cyclophilin A-ligand complexes of m/z 1751 by elimination of CO2 and of m/z 1749 by loss of CO2 and H2O or glycerol. Since immunosuppressive activity is known to be dependent on the formation of a binary complex between cyclophilin A and the drug and since the target for the binary complex was found to be the calcium- and calmodulin-dependent protein phosphatase, calcineurin, it could be interesting to measure for structurally related immunosuppressive drugs the CID energy necessary to dissoc. the binary complexes in order to evaluate whether a correlation with the phosphatase activity could be

derived.
ST IMM125 metabolite liver microsome immunosuppressant
IT Cyclophilins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(A; isolation, identification and immunosuppressive activity of IMM-125 metabolite from human liver microsomes)
IT Immunosuppressants
Liver
Microsome
(isolation, identification and immunosuppressive activity of IMM-125 metabolite from human liver microsomes)
IT 9025-75-6, Calcineurin
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(inhibition of; isolation, identification and immunosuppressive activity of IMM-125 metabolite from human liver microsomes)
IT **219740-62-2P**
RL: ANT (Analyte); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); MFM (Metabolic formation); PUR (Purification or recovery); ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation)
(isolation, identification and immunosuppressive activity of IMM-125 metabolite from human liver microsomes)
IT 135548-15-1, IMM 125
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(isolation, identification and immunosuppressive activity of IMM-125 metabolite from human liver microsomes)
IT 162936-12-1
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(isolation, identification and immunosuppressive activity of IMM-125 metabolite from human liver microsomes)
RE.CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Amar-Costesec, A; J Biol Chem 1974, V61, P201 HCAPLUS
(2) Braun, W; FASEB J 1995, V9, P63 HCAPLUS
(3) Bruelisauer, A; Drug Metab Dispos 1994, V22, P194 HCAPLUS
(4) Dieden, R; Xenobiotica 1997, V27, P933 HCAPLUS
(5) Ganem, B; J Am Chem Soc 1991, V113, P6294 HCAPLUS
(6) Hiestand, P; Transplant Proc 1992, V24(Suppl 2), P31
(7) Lowry, O; J Biol Chem 1951, V193, P265 HCAPLUS
(8) Mason, J; Pharmacol Rev 1989, V42, P423
(9) Omura, T; J Biol Chem 1964, V239, P2370 MEDLINE
(10) Schreier, M; Transplant Proc 1992, V24(Suppl 2), P19
(11) Taylor, P; Prog Biophys Mol Biol 1997, V67, P155 HCAPLUS
(12) Vickers, A; Drug Metab Dispos 1995, V23, P321 HCAPLUS
(13) Wagner, O; Drug Metab Dispos 1987, V15, P377 HCAPLUS
(14) Walkinshaw, M; Transplant Proc 1992, V24(Suppl 2), P8
(15) Wilm, M; J Mass Spectrom Ion Processes 1994, V136, P167 HCAPLUS

L44 ANSWER 5 OF 29 HCAPLUS COPYRIGHT 2002 ACS
AN 1996:306593 HCAPLUS
DN 125:6043
TI Controlling protein association and subcellular localization with a synthetic ligand that induces heterodimerization of proteins
AU Belshaw, Peter J.; Ho, Steffan N.; Crabtree, Gerald R.; Schreiber, Stuart L.
CS Howard Hughes Medical Institute, Harvard University, Cambridge, MA, 02138, USA

SO Proceedings of the National Academy of Sciences of the United States of America (1996), 93(10), 4604-4607
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
CC 13-1 (Mammalian Biochemistry)
AB Extracellular growth and differentiation factors induce changes in gene expression in the nucleus by initiating a series of protein assocns. that alter the subcellular localization of intracellular signaling proteins. Initial events involve receptor homo- or heterodimerization and subsequent recruitment of cytosolic signaling proteins to the inner leaflet of the plasma membrane. Intermediate events involve the translocation of proteins into the nucleus. Late events involve the recruitment of transcriptional activators to the vicinity of specific genes in the nucleus, resulting in increased gene transcription. The ability to induce signals at each of these three phases of signaling pathways is illustrated by the use of a heterodimeric chem. inducer of dimerization that causes a proximal relation between two different target proteins.
ST protein heterodimerization ligand synthesis
IT Proteins, specific or class, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(GF3'; controlling protein assocn. and subcellular localization with a synthetic ligand that induces heterodimerization of proteins)
IT Proteins, specific or class, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(JC3E; controlling protein assocn. and subcellular localization with a synthetic ligand that induces heterodimerization of proteins)
IT Molecular association
Signal transduction, biological
(controlling protein assocn. and subcellular localization with a synthetic ligand that induces heterodimerization of proteins)
IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(FA, controlling protein assocn. and subcellular localization with a synthetic ligand that induces heterodimerization of proteins)
IT 177080-80-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis if FKCsA, a ligand which induces heterodimerization of proteins)
IT 138957-22-9 177080-79-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis if FKCsA, a ligand which induces heterodimerization of proteins)
IT 162926-18-3P **177080-78-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis if FKCsA, a ligand which induces heterodimerization of proteins)

L44 ANSWER 6 OF 29 HCAPLUS COPYRIGHT 2002 ACS
AN 1996:156367 HCAPLUS
DN 124:306383
TI A rifampicin-induced hepatic microsomal enzyme system for the generation of cyclosporine metabolites
AU Tamolang, M. B.; Liu, W. T.; Pang, H.; Ren, Ying; Wong, P. Y.
CS Department of Clinical Biochemistry, University of Toronto, Toronto, ON, Can.

SO Pharmacological Research (**1995**), 32(3), 141-8
CODEN: PHMREP; ISSN: 1043-6618
PB Academic
DT Journal
LA English
CC 1-2 (Pharmacology)
Section cross-reference(s): 9

AB A drug-induced rabbit hepatic microsomal enzyme system has been developed to produce milligram quantities of cyclosporine metabolites (CMs). Using a rifampicin-induced microsomal prepn. in the presence of a NADPH regenerating system, 60% of the cyclosporine (CsA) was converted to CMs in 2 h. The CMs were recovered by solid phase extn., and sepd. by gradient high performance liq. chromatog. with two Ultrasphere Ocyl (C8) columns connected in tandem. More than 20 CMs were resolved. The quantities of major CMs produced by 45 mg of microsomal proteins were established by comparing peak areas with known concns. of authentic CM stds. These major CMs included AM1, AM9, AM19, AM4N, AM1c and the aldehydic isomers (AM1cAL plus AM1AL). Other CMs that were not quantified included AM14N, AM4N9, AM1A, AM1c9, and AM1D1. Several CMs remained to be identified. All CMs were detected by RIA using a non-specific CsA antiserum. The purity of the CMs were confirmed by fast at. bombardment mass spectrometry. Similar findings were obsd. when erythromycin or troleandomycin was used to induce the hepatic microsomal enzymes. The procedure used to generate CMs was simple. With the enzyme fraction derived from one rabbit liver, 90 to 100 mg of CMs can be obtained. In this study, the metabolite patterns of CsA produced by rabbit liver microsomes were shown to resemble those obsd. for humans. These results indicate the possibility of using rabbit models to predict CsA biotransformation in man. The CMs generated by this enzyme system can be used to acquire information relevant to the situation in man.

ST cyclosporine metabolite generation liver microsome enzyme; biotransformation cyclosporine liver microsome enzyme

IT Drug biotransformation
(rabbit model for prediction of biotransformation in humans; use of a rifampicin-induced hepatic microsomal enzyme system for generation of cyclosporine metabolites)

IT Immunosuppressants
Liver
Microsome
(use of a rifampicin-induced hepatic microsomal enzyme system for generation of cyclosporine metabolites)

IT 9035-51-2, Cytochrome P 450, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); CAT (Catalyst use); BIOL (Biological study); PROC (Process); USES (Uses)
(IIIA; use of a rifampicin-induced hepatic microsomal enzyme system for generation of cyclosporine metabolites)

IT 114-07-8, Erythromycin 2751-09-9, Troleandomycin 13292-46-1, Rifampicin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(use of a rifampicin-induced hepatic microsomal enzyme system for generation of cyclosporine metabolites)

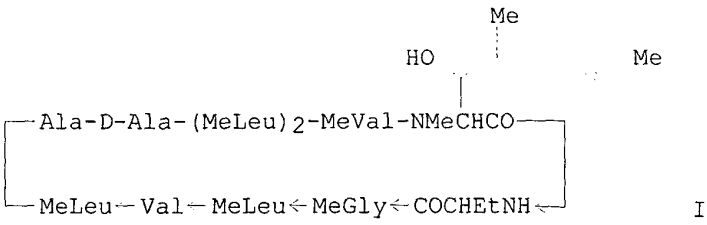
IT 59865-13-3DP, Cyclosporine, metabolites 89270-23-5P, AM 4N 89270-25-7P, AM 9 89270-26-8P, AM 19 89270-28-0P, AM 1 89270-29-1P, AM 1c **100364-58-7P**, AM 1A 107335-27-3P, AM 14N 107335-28-4P, AM 1c9 112077-93-7P, AM 4N9 121886-75-7P, AM 1D1 176365-87-0P, AM 1AL 176365-88-1P, AM 1cAL
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); MFM (Metabolic formation); PUR (Purification or recovery); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation)
(use of a rifampicin-induced hepatic microsomal enzyme system for

generation of cyclosporine metabolites)
IT 59865-13-3, Cyclosporine
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(use of a rifampicin-induced hepatic microsomal enzyme system for generation of cyclosporine metabolites)

L44 ANSWER 7 OF 29 HCAPLUS COPYRIGHT 2002 ACS
AN 1992:483083 HCAPLUS
DN 117:83083
TI The synergistic immunosuppressive potential of cyclosporin metabolite combinations
AU Radeke, Heinfried H.; Christians, Uwe; Sewing, Karl F.; Resch, Klaus
CS Inst. Molekularpharmakol., Med. Hochsch., Hannover, D-3000/61, Germany
SO International Journal of Immunopharmacology (**1992**), 14(4), 595-604
CODEN: IJIMDS; ISSN: 0192-0561
DT Journal
LA English
CC 1-7 (Pharmacology)
AB Of the 29 cyclosporin (CS) metabolites defined so far, 7 representatives were isolated from the bile of liver grafted patients, purified by HPLC, and characterized by FAB-MS and/or 1H-NMR. These were used to det. the growth inhibitory effects on Con A-stimulated rat lymph node (LN) lymphocytes. Metabolites dild. in culture medium at concns. rechecked by HPLC at the resp. assay time were added and proliferation detd. by [3H]thymidine incorporation after 48 h. A 50% growth inhibition of LN by single metabolites (AM) was achieved at the following concns. (mg/L): CS, 0.023; primary metabolites AM1, 0.11; AM1c, 0.65; AM9, 1.05; secondary metabolites AM19, 1.02; AM4N9, 1.02; H355, 1.85; and AM1A, 4.5. Although all metabolites were immunosuppressive at higher concns. in vitro on a single metabolite level, only AM1, with 20% of the activity of native CS, seemed to play a role in vivo. However, when the antiproliferative effects were tested on double or triple metabolite combinations, a strong synergism was found not only of primary metabolites, but even with combinations including secondary metabolites. The concn. of the participating metabolites necessary to decrease LN growth by 50% was far below the trough levels obsd. in vivo. Finally, to mimic to some extent the in vivo situation, the interaction of native CS with single metabolites or double combinations was studied. In contrast to the clear synergism in the absence of CS, the combinations of metabolites with native CS resulted in an additive growth inhibition. These results indicate an immunosuppressive potential of all metabolites tested and a clear synergism of metabolites in the absence of CS. Although up to double metabolite combinations did only additively enhance CS-induced immunosuppression, the combination of 29 metabolites occurring in vivo might have significant immunosuppressive effects in situations where CS levels drop below active concns.
ST cyclosporin metabolite immunosuppression synergism
IT Immunosuppressants
(cyclosporin and metabolites, synergistic potential of)
IT Lymphocyte
(cyclosporin metabolite synergistic immunosuppressive potential on)
IT Drug interactions
(synergistic, of cyclosporin and metabolites, on immunosuppression)
IT 59865-13-3, Cyclosporin 89270-25-7 89270-26-8 89270-28-0 89270-29-1 **100364-58-7** 112077-93-7 142785-21-5, Cyclosporin A metabolite H 355
RL: BIOL (Biological study)
(immunosuppressive activity of, cyclosporin metabolite combinations synergistic effects on)
IT 59865-13-3D, Cyclosporin, metabolites
RL: PRP (Properties)

(synergistic immunosuppressive potential of)

L44 ANSWER 8 OF 29 HCAPLUS COPYRIGHT 2002 ACS
AN 1992:15264 HCAPLUS
DN 116:15264
TI Investigations on the metabolic pathways of cyclosporine: I. Excretion of cyclosporine and its metabolites in human bile - isolation of 12 new cyclosporine metabolites
AU Christians, U.; Strohmeyer, S.; Kownatzki, R.; Schiebel, H. M.; Bleck, J.; Greipel, J.; Kohlhaw, K.; Schottmann, R.; Sewing, K. F.
CS Inst. Allg. Pharmakol., Med. Hochsch. Hannover, Hannover, Germany
SO Xenobiotica (**1991**), 21(9), 1185-98
CODEN: XENOBH; ISSN: 0049-8254
DT Journal
LA English
CC 1-2 (Pharmacology)
GI




I

AB Cyclosporine (I) metabolites of known and unknown structures were isolated by semipreparative HPLC from human bile from the T-tube of liver-grafted patients who received cyclosporine treatment. Their structures were elucidated by FAB mass spectrometry and 1H-NMR spectroscopy. Twelve of the cyclosporine metabolites, with known chem. structures, were isolated and identified using authentic std. material. Four isolated fractions contained trihydroxylated metabolites; two fractions contained dihydroxylated, demethylated, metabolites; one fraction contained a trihydroxylated, demethylated metabolite; and one fraction a monohydroxylated, demethylated metabolite. The exact metab. sites were partially defined. Two carboxylated cyclosporine metabolites, of which one was hydroxylated in an unknown position, were isolated. One new metabolite proved to be a glucuronylated phase II metabolite. Deglucuronylation of this metabolite by .beta.-glucuronidase yielded metabolite AM1c. The proposed structure was AM1c-glucuronide; is a proposed extension of the Hawk's Cay nomenclature of the cyclosporine metabolites for glucuronylated metabolites. One of the unknown metabolites was hydroxylated in two positions of amino acid 1. The proposed nomenclature was 'AM11d', where '1d' indicates hydroxylation of the .delta.C of amino acid 1. A metabolite with an aldehyde functional group at amino acid 1, which had two isomeric forms, was isolated. I.r.-spectroscopy indicated that isomerism may be caused by conjugation of the aldehyde group with the double bond between C6 and C7 of amino acid 1.
ST cyclosporine metab bile
IT Bile
(cyclosporine and its metabolites of human)
IT 89270-23-5 89270-24-6 89270-25-7 89270-26-8 89270-27-9
89270-28-0 89270-29-1 89288-32-4 **100364-58-7** 107335-27-3
107335-28-4 112077-93-7 129843-36-3 137459-34-8 137459-35-9
137459-36-0 137483-88-6 137483-89-7 137500-55-1 137500-58-4
137500-59-5
RL: BIOL (Biological study)
(as cyclosporine metabolite, in bile of humans)

IT 59865-13-3, Cyclosporine
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metab. of, in humans, metabolites in bile in)

L44 ANSWER 9 OF 29 HCAPLUS COPYRIGHT 2002 ACS
AN 1991:670244 HCAPLUS
DN 115:270244
TI Synergistic and antagonistic effects of combinations of cyclosporine A and its metabolites on inhibition of phytohemagglutinin-induced lymphocyte transformation in vitro
AU Schultz, John C.; Lensmeyer, Gary L.; Wendal, Thad D.; Shahidi, Nasrollah T.; Wiebe, Donald A.; Carlson, Ian H.
CS Div. Pediatr. Hematol./Oncol., Univ. Wisconsin, Madison, WI, 53792, USA
SO Biochemical Pharmacology (**1991**), 42(7), 1403-10
CODEN: BCPCA6; ISSN: 0006-2952
DT Journal
LA English
CC 1-7 (Pharmacology)
AB Cyclosporine A (CsA) and purified CsA metabolites were tested alone and in combinations in cell cultures to det. their effects on PHA-induced human lymphocyte proliferation. CsA was more inhibitory than its metabolites at all concns. tested (0-1000 ng/mL). CsA exerted a max. inhibition (70% decrease in [Me-3H]thymidine incorporation) at concns. .gtoreq.300 ng/mL; metabolites M1, M17, and M21 depressed the response 46, 39, and 23%, resp., at 300 ng/mL. Metabolites M8, M18, M26, M25, M13, and M203-218 were noninhibitory. When combinations of M17 and CsA were tested, a synergistic effect occurred at combinations of low concns. of M17 and CsA and an antagonistic effect at higher concns. Of the 49 combinations of CsA and M17 tested, 30 were antagonistic, 16 synergistic, and 3 undecided (approaching additivism). When 49 combinations of CsA and the non-immunosuppressive metabolite M8 were tested, 29 combinations were synergistic, 17 antagonistic, 1 additive, and 2 undecided. Of the 29 synergistic combinations, 14 were strongly synergistic. The importance of interactions of CsA and its metabolites to the immunopharmacol. of CsA therapy is discussed.
ST cyclosporine metabolite interaction lymphocyte immunosuppression
IT Immunosuppressants
(cyclosporin A and metabolites as, in lymphocytes of human, interactions in)
IT Lymphocyte
(cyclosporin A and metabolites immunosuppression of human, interactions in)
IT Drug interactions
(of cyclosporin A, with metabolites, lymphocyte immunosuppression response to, in human)
IT 59865-13-3D, Cyclosporin A, derivs. 89270-23-5 89270-25-7 89270-26-8 89270-28-0 89270-29-1 **100364-58-7** 107335-27-3 107335-28-4
RL: BIOL (Biological study)
(immunosuppressant effects of cyclosporin A and metabolite, interactions in)
IT 59865-13-3, Cyclosporin A
RL: PRP (Properties)
(interaction of, with metabolites, lymphocyte immunosuppression response to, in human)

L44 ANSWER 10 OF 29 HCAPLUS COPYRIGHT 2002 ACS
AN 1991:669869 HCAPLUS
DN 115:269869
TI Investigations on the metabolic pathways of cyclosporine: II. Elucidation of the metabolic pathways in vitro by human liver microsomes
AU Christians, U.; Strohmeyer, S.; Kownatzki, R.; Schiebel, H. M.; Bleck, J.; Kohlhaw, K.; Schottmann, R.; Sewing, K. F.

CS Inst. Allg. Pharmakol., Med. Hochsch. Hannover, Hannover, Germany
SO Xenobiotica (**1991**), 21(9), 1199-210
CODEN: XENOBH; ISSN: 0049-8254
DT Journal
LA English
CC 1-2 (Pharmacology)
AB Cyclosporine and its metabolites, isolated from human bile and identified by FAB mass spectrometry and 1H-NMR spectroscopy, were metabolized by human liver microsomes for the identification of new cyclosporine metabolites. From these data a metabolic pathway for cyclosporine, which includes these new cyclosporine metabolites, has been proposed. The new metabolites were isolated by semipreparative HPLC and their chem. structures were elucidated by FAB mass spectrometry. These isolated metabolites were further metabolized and the products identified by FAB mass spectrometry. Fourteen metabolites, whose structure has not yet been elucidated, were isolated after metab. of structurally identified cyclosporine metabolites, and chem. structures for five of these metabolites were proposed. The structures of the new cyclosporine metabolites were: (i) a N-demethylated, carboxylated deriv. (AM1A4N), (ii) a di-hydroxylated, N-demethylated deriv. (AM14N9), (iii) a hydroxylated and carboxylated deriv. (AM1A9), (iv) a dihydroxylated, cyclized and N-demethylated deriv. (AM1c4N9) and (v) a cyclized and carboxylated (AM1cA) deriv. A proposed cyclosporine metabolic pathway comprises a total of 29 metabolites. It consists of four main branches originating from metabolites AM1, AM1c, AM9, and AM4N.
ST cyclosporine metab liver microsome
IT Microsome
(cyclosporine metab. by human liver)
IT Liver, metabolism
(cyclosporine metab. by microsomes of human)
IT 89270-23-5 89270-25-7 89270-26-8 89270-27-9 89270-28-0
89270-29-1 89288-32-4 **100364-58-7** 107335-28-4 112077-93-7,
Cyclosporin A metabolite 4N9 119386-81-1, Cyclosporin A metabolite 14N9
129843-36-3, Cyclosporin A metabolite 1AL 137500-55-1, Cyclosporin A
metabolite 11d 137500-56-2, Cyclosporin A metabolite 1A4N 137500-57-3,
Cyclosporin A metabolite 1A9 137500-58-4, Cyclosporin A metabolite 1Ac
137500-59-5 137500-60-8, Cyclosporin A metabolite 1c4N9
RL: BIOL (Biological study)
(as cyclosporine metabolite, in liver microsómes of humans)
IT 59865-13-3, Cyclosporine
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metab. of, by liver microsomes of humans)

L44 ANSWER 11 OF 29 HCAPLUS COPYRIGHT 2002 ACS
AN 1991:549642 HCAPLUS
DN 115:149642
TI Micro-quantification of cyclosporine and its metabolites and determination of their spectral absorptivities
AU Fu, Irong; Bowers, Larry D.
CS Dep. Lab. Med. Pathol., Univ. Minnesota, Minneapolis, MN, 55455, USA
SO Clinical Chemistry (Washington, DC, United States) (**1991**), 37(7), 1185-90
CODEN: CLCHAU; ISSN: 0009-9147
DT Journal
LA English
CC 1-1 (Pharmacology)
AB A micromethod for the anal. of cyclosporine (CsA), based on quantification of its constituent amino acids is reported. The amino acids were released by gas-phase hydrolysis, derivatized with fluorenylmethyl chloroformate, and sepd. and analyzed in a reversed-phase HPLC system. The imprecision (CV) of the amino acid anal. was <4%, and several detns. of the amt. of std. CsA were within 1% of the weighed material. The detection limits

(signal-to-noise ratio = 2) were 500 fmoll for UV detection and 100 fmol for fluorescence detection. This method was also used to det. the UV absorptivities of CsA and five metabolites at 210, 214, and 230 nm. The molar absorptivity of most metabolites was about 10% higher than that of CsA, although the metabolite that was oxidized to a carboxyl group on the terminal carbon of N-methylbutenylmethylthreonine (AM1A) had a molar absorptivity about 40% higher than that of CsA.

ST cyclosporine metabolite detn HPLC fluorometry; liq chromatog cyclosporine metabolite

IT Spectrochemical analysis
(UV, in cyclosporine and its metabolites detn.)

IT Spectrochemical analysis
(fluorometric, in cyclosporine and its metabolites detn.)

IT Chromatography, column and liquid
(high-performance, reversed-phase, in cyclosporine and its metabolites detn.)

IT 89270-23-5 89270-25-7 89270-26-8 89270-28-0 **100364-58-7**
RL: ANT (Analyte); ANST (Analytical study)
(detn. of, as cyclosporine metabolite, by HPLC)

IT 59865-13-3, Cyclosporine
RL: ANT (Analyte); ANST (Analytical study)
(detn. of, by HPLC, metab. in relation to)

L44 ANSWER 12 OF 29 HCAPLUS COPYRIGHT 2002 ACS

AN 1991:505665 HCAPLUS

DN 115:105665

TI Assessment of the biological activity of cyclosporine metabolites using the human JURKAT cell line

AU Freed, B. M.; Stevens, C.; Brooks, C.; Cramer, S.; Lempert, N.; Rosano, T. G.

CS Dep. Surg., Albany Med. Coll., Albany, NY, 12208, USA

SO Transplantation Proceedings (**1991**), 23(1, Bk. 2), 980-1
CODEN: TRPPA8; ISSN: 0041-1345

DT Journal

LA English

CC 1-7 (Pharmacology)

AB In the human leukemia T-cell line JURKAT 6.8, the most potent of the cyclosporine metabolites had approx. 10% of the immunosuppressive activity of the parent compds., whereas the other metabolites were less potent or inactive. The results highlight the need to assess the effects of the metabolites in vivo.

ST cyclosporine metabolite immunosuppressant T lymphocyte

IT Immunosuppressants
(cyclosporine and its metabolites as, in T-lymphocytes of humans)

IT Lymphocyte
(T-, cyclosporine and its metabolites immunosuppressant activity in human)

IT 89270-25-7 89270-26-8 89270-28-0 89270-29-1 **100364-58-7**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(immunosuppressant activity of, as cyclosporine metabolite, in T-lymphocytes of humans)

IT 59865-13-3D, Cyclosporine, metabolites
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(immunosuppressant activity of, in T-lymphocytes of humans)

IT 59865-13-3, Cyclosporine
RL: BIOL (Biological study)
(immunosuppression from, in T-lymphocytes of humans, metabolites in)

L44 ANSWER 13 OF 29 HCAPLUS COPYRIGHT 2002 ACS

AN 1991:464248 HCAPLUS
DN 115:64248
TI Additive and synergistic effects of cyclosporine metabolites on glomerular mesangial cells
AU Radeke, Heinfried H.; Christians, Uwe; Bleck, Joerg S.; Sewing, Karl F.; Resch, Klaus
CS Abt. Molekularpharmakol., Med. Hochsch., Hannover, D-3000/61, Germany
SO Kidney International (**1991**), 39(6), 1255-66
CODEN: KDYIA5; ISSN: 0085-2538
DT Journal
LA English
CC 1-7 (Pharmacology)
AB Out of the 29 cyclosporine (Cs) metabolites defined so far, 10 representative ones were isolated from bile of liver grafted patients, purified by HPLC, and their structure specified by FAB-MS and 1H NMR. These were used to det. the growth inhibitory effects on Sprague Dawley rat glomerular mesangial cells (MC). Metabolite dilns. were added to cultured MC for 72 h and [3H]thymidine incorporation was measured. A 50% growth inhibition by single metabolites (M) on MC was achieved at the following concns. (mg/L): Cs: 1.25; M21: 6.0; M18: 9.0; M26: 10.5; M1: 10.8; M8: 10.8; M17: 12.5; M13: >20.0; M25: >25.0; M203-218: >50.0; H355: >50.0. The activity was correlated to the degree of metabolization as the group of six "active" compds. included 4 primary metabolites (hydroxylated or demethylated derivs. of Cs: M21, M18, M1, M17), whereas the 4 "inactive" compds. exclusively were secondary metabolites (demethylated, hydroxylated and/or oxidized primary metabolites: M13, M25, M203-218, H355). Combinations of active metabolites with or without Cs resulted in an additive antiproliferative effect. Although single metabolite activities are not relevant in vivo, already combinations of 3 (M1 + M17 + M18) or 4 metabolites (M17 + M18 + M21 + H355) resulted in a significant growth inhibition at concns. of the participating metabolites measured in urine of liver transplanted patients. Moreover, significant synergistic activities were detd. with combinations including secondary metabolites. A final set of expts. discharged unspecific cytotoxic effects. The inhibition of MC [3H]thymidine incorporation was completely reversible and moreover, direct mesangiolysis was excluded for both single and combined metabolite actions. Thus, considering rat MC proliferation as an initial kidney cell model system for subsequent, more detailed studies measuring functional parameters, it was demonstrated that activities of single metabolites are related to their chem. structure. More importantly, mimicking to some extent the patients' situation, combinations of metabolites at concns. occurring in vivo reduced MC proliferation in culture in an at least additive fashion, suggesting that side effects of Cs treatment might be attributed to combined Cs metabolite actions.
ST cyclosporin A metabolite kidney mesangium toxicity
IT Kidney, toxic chemical and physical damage
(mesangium, cyclosporin A metabolites toxicity to, additive and synergistic effects in)
IT 89270-23-5P 89270-25-7P 89270-26-8P 89270-28-0P 89270-29-1P **100364-58-7P** 107335-27-3P 107335-28-4P 135125-20-1P 135160-89-3P
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and toxicity of, as cyclosporin A metabolite to glomerular mesangial cells)
IT 59865-13-3, Cyclosporin A
RL: PRP (Properties)
(toxicity of, to glomerular mesangial cells)
IT 59865-13-3D, Cyclosporin A, metabolites
RL: PRP (Properties)
(toxicity of, to glomerular mesangial cells, additive and synergistic effects in)

L44 ANSWER 14 OF 29 HCAPLUS COPYRIGHT 2002 ACS

AN 1990:565083 HCAPLUS
DN 113:165083
TI Biologic activity of cyclosporine metabolites
AU Sewing, K. F.; Christians, U.; Kohlhaw, K.; Radeke, H.; Strohmeyer, S.; Kownatzki, R.; Budniak, J.; Schottmann, R.; Bleck, J. S.; et al.
CS Abt. Allg. Pharmakol., Med. Hochsch., Hannover, D-3000/61, Germany
SO Transplantation Proceedings (**1990**), 22(3), 1129-34
CODEN: TRPPA8; ISSN: 0041-1345
DT Journal
LA English
CC 1-7 (Pharmacology)
AB The authors studied nephrotoxicity of cyclosporine (CyA) and its metabolites in liver graft patients. There were no differences in patients with or without CyA nephrotoxicity with respect to CyA doses, coadministered nephrotoxic drugs, liver parameters, kidney function before transplantation, and CyA trough levels in blood. The only independent variable in this study influencing CyA nephrotoxicity was the CyA metabolite pattern. There was a high correlation between CyA nephrotoxicity and the double hydroxylated CyA metabolites, esp. with the double hydroxylated and cyclizated metabolite H270(26), but not with CyA itself. The CyA metabolite toxicity detected seemed to be the result of a characteristic cytochrome P 450 isoenzyme pattern of patients developing CyA nephrotoxicity. The alteration of the CyA metabolite pattern by rejection or cholestasis resulted in an increase in concn. of the metabolites H250(8) and H350(203-218) in blood and urine. The other metabolites were not affected. The metabolite pattern is similar during acute rejection and cholestasis. It is different from that characteristic of for CyA metabolite toxicity since there is no increase in cyclizated metabolites. Both metabolite patterns have an elevated concn. of metabolite H240(8) in common. It is possible that metabolite H250(8) is directly cyclized to metabolite H270(26). Whether this is of clin. importance remains to be evaluated.
ST cyclosporine metabolite kidney toxicity
IT Kidney, toxic chemical and physical damage
(cyclosporine toxicity to, metabolites in, in liver transplantation in humans)
IT Transplant and Transplantation, animal
(of liver, cyclosporine metab. and kidney toxicity in, in humans)
IT Liver
(transplant, cyclosporine metab. and kidney toxicity in, in humans)
IT 89270-23-5 89270-24-6 89270-25-7 89270-26-8 89270-27-9 89270-28-0 89270-29-1 89288-32-4 **100364-58-7** 107335-27-3 107335-28-4 129843-36-3
RL: BIOL (Biological study)
(as cyclosporine metabolite, kidney toxicity in relation to, in liver transplantation in humans)
IT 59865-13-3D, Cyclosporin A, metabolites
RL: FORM (Formation, nonpreparative)
(formation of, kidney toxicity in relation to, in liver transplantation in humans)
IT 59865-13-3, Cyclosporine
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metab. of, kidney toxicity and pharmacol. in human in relation to, in liver transplants.)

L44 ANSWER 15 OF 29 HCAPLUS COPYRIGHT 2002 ACS
AN 1990:545029 HCAPLUS
DN 113:145029
TI Sandimmun metabolites: their potential to cause adverse reactions in the rat
AU Donatsch, P.; Rickenbacher U.; Ryffel, B.; Brouillard, J. F.
CS Dep. Drug Saf. Assess., Sandoz, Basel, CH-4002, Switz.

SO Transplantation Proceedings (**1990**), 22(3), 1137-40
CODEN: TRPPA8; ISSN: 0041-1345
DT Journal
LA English
CC 1-7 (Pharmacology)
AB The toxic effects of Sandimmum cyclosporin (CyA) and its 4 metabolites were studied in spontaneously hypertensive rats. The metabolites 17, 18, 21, and 203-318 had no nephrotoxic and/or hepatotoxic potential. There was no evidence of immunosuppressive activity of the 4 metabolites. The exposure of the animals to the various compds. expressed as area under the curve value or mean plasma level differed markedly, being highest for CyA and 203-318, followed by metabolites 18, 17, and 21.
ST Sandimmun metabolite toxicity liver kidney; cyclosporin A metabolite toxicity liver kidney
IT Kidney, toxic chemical and physical damage
Liver, toxic chemical and physical damage
(cyclosporin A metabolites toxicity to)
IT 89270-23-5, Cyclosporin A metabolite 21 89270-28-0, Cyclosporin A metabolite 17 89270-29-1, Cyclosporin A metabolite 18
**100364-58-7**, Cyclosporin A metabolite 203-218
RL: PRP (Properties)
(toxicity of, to kidney and liver)
IT 59865-13-3, Cyclosporin A
RL: PRP (Properties)
(toxicity of, to kidney and liver, metabolites in relation to)

L44 ANSWER 16 OF 29 HCAPLUS COPYRIGHT 2002 ACS
AN 1990:526201 HCAPLUS
DN 113:126201
TI Studies on the biologic activities of Sandimmun metabolites in humans and in animal models: review and original experiments
AU Fahr, A.; Hiestand, P.; Byffel, B.
CS Dep. Pharmacol. Dev. Preclin. Res., Sandoz Pharm. Ltd., Basel, Switz.
SO Transplantation Proceedings (**1990**), 22(3), 1116-24
CODEN: TRPPA8; ISSN: 0041-1345
DT Journal; General Review
LA English
CC 1-7 (Pharmacology)
AB Expts. from the authors' lab. on information on the immunosuppressive activity of cyclosporin A (CyA) metabolites are described. An overview of the available information about the immunosuppressive activity of CyA metabolites is given.
ST Sandimmun metabolite pharmacol; review cyclosporine metabolite pharmacol
IT Immunosuppressants
(cyclosporine and metabolites as, in humans and lab. animals)
IT 89270-23-5 89270-28-0 89270-29-1 **100364-58-7**
RL: BIOL (Biological study)
(as cyclosporine metabolite, immunosuppressive activity and pharmacol. of, in humans and lab. animals)
IT 59865-13-3, Cyclosporin A
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metab. and immunosuppressive activity of, in humans and lab. animals)

L44 ANSWER 17 OF 29 HCAPLUS COPYRIGHT 2002 ACS
AN 1990:91112 HCAPLUS
DN 112:91112
TI Three commercial polyclonal immunoassays for cyclosporin A in whole blood compared: 2. Cross-reactivity of the antisera with cyclosporin A metabolites
AU Lensmeyer, Gary L.; Wiebe, Donald A.; Carlson, Ian H.; DeVos, Diane J.
CS Dep. Pathol. Lab. Med., Univ. Wisconsin, Madison, WI, 53792, USA
SO Clinical Chemistry (Washington, DC, United States) (**1990**),

36(1), 119-23
CODEN: CLCHAU; ISSN: 0009-9147
DT Journal
LA English
CC 1-1 (Pharmacology)
AB The authors demonstrate the diverse selectivity of three com. polyclonal "cyclosporine" immunoassays for cyclosporin A (CsA) metabolites by comparing anal. responses of nine metabolites added to drug-free whole-blood specimens (range 0 to 2000 .mu.g/L) and assayed by the Abbott TDx fluorescence polarization immunoassay (FPIA), the Incstar Cyclo-Trac RIA (RIA), and the Sandoz RIA. Cross-reactivity-defined as the relative response (slope of regression line) of metabolite/parent CsA over the assay's linear range of concns.-differed for each metabolite among the three assays. Overall, Abbott's antiserum exhibited the greatest affinity for the metabolites, the Sandoz antiserum the least. Ranges of cross-reactivity for the metabolites over all three assays were M1 (14-44%), M8 (9-20%), M13 (13-26%), M17 (50-116%), M18 (17-79%), M21 (4-54%), M25 (<1-52%), M26 (<1-29%), and M203-218 (7-51%). The specificities of the Abbott, Incstar, and Sandoz polyclonal assays thus differ significantly, and this brings into question the practical utility of comparing data generated for patients' specimens by different procedures.
ST cyclosporin A metabolite blood polyclonal immunoassay
IT Antiserums
(to cyclosporin A, in polyclonal immunoassays, cross-reactivity with cyclosporin A metabolites of)
IT Immunochemical analysis
(immunoassay, polyclonal, cyclosporin A metabolites detn. in human blood by three, comparison of, cross-reactivity of antiserum in relation to)
IT 59865-13-3D, Cyclosporin A, metabolites
RL: ANT (Analyte); ANST (Analytical study)
(detn. of, in human blood by three polyclonal immunoassays, cross-reactivity of antiserum in)
IT 89270-23-5, Cyclosporin A metabolite 21 89270-25-7, Cyclosporin A metabolite 1 89270-26-8, Cyclosporin A metabolite 8 89270-28-0, Cyclosporin A metabolite 17 89270-29-1, Cyclosporin A metabolite 18 **100364-58-7**, Cyclosporin A metabolite 203-218 107335-27-3, Cyclosporin A metabolite 25 107335-28-4, Cyclosporin A metabolite 26
RL: ANT (Analyte); ANST (Analytical study)
(detn. of, in human blood by three polyclonal immunoassays, cross-reactivity of antiserum with cyclosporin A metabolites in)

L44 ANSWER 18 OF 29 HCAPLUS COPYRIGHT 2002 ACS
AN 1989:546244 HCAPLUS
DN 111:146244
TI Urinary excretion of cyclosporin and 17 of its metabolites in renal allograft recipients
AU Bleck, J. S.; Schlitt, H. J.; Christians, U.; Thiesemann, C.; Strohmeyer, S.; Schottmann, R.; Kohlhaw, K.; Wonigeit, K.; Sewing, K. F.
CS Abt. Allg. Pharmakol., Med. Hochsch. Hannover, Hannover, D-3000/61, Fed. Rep. Ger.
SO Pharmacology (**1989**), 39(3), 160-4
CODEN: PHMGBN; ISSN: 0031-7012
DT Journal
LA English
CC 1-2 (Pharmacology)
AB Renal elimination of the immunosuppressant cyclosporin is virtually unknown. Therefore, in renal allograft recipients under steady-state conditions, the urinary excretion of cyclosporin and 17 of its metabolites in blood and 24-h urine was studied. Cyclosporin and its metabolites were measured by HPLC. Metabolite but not cyclosporin excretion was strongly correlated with creatinine clearance. Metabolites 18 and 26

(.beta.,.epsilon.-cyclic metabolite) were rarely found in blood but were excreted in considerable amts. in urine. Approx. 3% of the administered dose of cyclosporin per day underwent renal elimination in unchanged form or as metabolites. There is glomerular filtration of cyclosporin metabolites, a difference in the rate of elimination between cyclosporin and the metabolites, and some kind of metab. or active transport mechanism for metabolites in the kidney.

ST cyclosporin metabolite urine excretion

IT Urine
(cyclosporine and metabolites excretion in human)

IT Blood
(cyclosporine and metabolites of human)

IT 89270-23-5, Cyclosporin A metabolite 21 89270-24-6, Cyclosporin A metabolite 9 89270-25-7, Cyclosporin A metabolite 1 89270-26-8, Cyclosporin A metabolite 8 89270-28-0, Cyclosporin A metabolite 17 89270-29-1, Cyclosporin A metabolite 18 89288-32-4, Cyclosporin A metabolite 10 **100364-58-7**, Cyclosporin A metabolite 203-218 107335-27-3, Cyclosporin A metabolite 25 107335-28-4, Cyclosporin A metabolite 26
RL: BIOL (Biological study)
(formation of and urinary excretion of, as cyclosporine metabolite, in humans)

IT 59865-13-3, Cyclosporin A
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metab. and urinary excretion of, in humans)

IT 59865-13-3D, Cyclosporin A, metabolites
RL: PROC (Process)
(urinary excretion of, in humans)

L44 ANSWER 19 OF 29 HCAPLUS COPYRIGHT 2002 ACS

AN 1989:527017 HCAPLUS

DN 111:127017

TI Fluorescence polarization immunoassay for cyclosporin A and metabolites based on novel cyclosporin A derivatives

IN Wang, Nai Yi; Wang, Philip P.; Morrison, Marjorie Anne

PA Abbott Laboratories, USA

SO Eur. Pat. Appl., 17 pp.
CODEN: EPXXDW

DT Patent

LA English

IC ICM C07K007-64
ICS G01N033-68; G01N033-58

CC 1-1 (Pharmacology)
Section cross-reference(s): 26

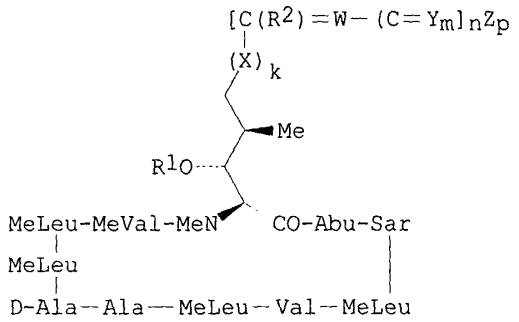
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | EP 283801 | A2 | 19880928 | EP 1988-103397 | 19880304 <-- |
| | EP 283801 | A3 | 19900530 | | |
| | R: BE, CH, DE, ES, FR, GB, IT, LI | | | | |
| | JP 63258491 | A2 | 19881025 | JP 1988-73057 | 19880325 <-- |
| | US 5239057 | A | 19930824 | US 1991-776890 | 19911015 <-- |
| | US 5427960 | A | 19950627 | US 1994-318570 | 19941005 <-- |

| | | | |
|---|---|---|---|
| PRAI | US 1987-31494 | 19870327 | <-- |
| | US 1989-376244 | 19890706 | <-- |
| | US 1991-776890 | 19911015 | <-- |
| | US 1993-60598 | 19930512 | <-- |

OS MARPAT 111:127017

GI



I

AB A method is described for prepn. of cyclosporin A derivs. I [k = 0-1 (k = 0 only if n = 1); m = 0-2; n, p = 0-1; R1 = H or a protecting group; R2 = H, lower alkyl, or CH(OH)Me; W = 1-20 (not including H) atoms of C, N, O, S, with .ltoreq.2 heteroatoms bonded together and with O never bonded to O or S; X = CH2, CHOH, C(O) (n = 0), or CH2OH (p = 0); Y = O, S, or NH; Z = a poly(amino acid), a poly(amino acid) deriv., a fluorescent moiety, OH, NH2, NHNH2, ORa, SRa, NHRa, NRaRb (Ra, Rb = stable C1-10 chain), SH, or a leaving group; MeVal, MeLeu, Sar, and Abu represent residues of N-methylvaline, N-methylleucine, sarcosine, and L-.alpha.-aminobutyric acid, resp.]. The derivs. are used as (1) immunogens in formation of antibodies specific to cyclosporin A and some metabolites, and (2) precursors in synthesis of fluorescent tracers having .gtoreq.1 epitope in common with cyclosporin A and some metabolites. Antibodies and tracers are employed in a fluorescence polarization immunoassay (FPIA) for cyclosporin A and metabolites in biol. fluids. [6-(Carboxymethyloximino)-3-(R)-hydroxy-4-(R)-methyl-2-(S)-methylaminohexanoyl]6cyclosporin A (I; k = 0; m, n, p = 1; R1, R2 = H; W = NOCH2; Y = O; Z = OH) (prepn. given) was conjugated to bovine serum albumin with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide-HCl, and the resulting immunogen was used to immunize exptl. animals. A fluorescent cyclosporin A tracer was prepd. from [7-carboxy-3-(R)-hydroxy-4-(R)-methyl-2-(S)-methylamino-6-heptenoyl]6cyclosporin A (I; k = 0; m, n, p = 1; R2 = H; W = CH; Y = O; Z = OH) and aminomethylfluorescein-HCl. To serum or plasma samples was added pptn. reagent (30 mM NH4OAc in 98.5% aq. Me2CHOH). Following mixing and centrifuging, samples were analyzed with an automated assay employing an Abbott TDx Analyzer and a Cyclosporin and Metabolites Reagent pack. FPIA sensitivity was 15 ng/mL for cyclosporin A and metabolites. In a comparison of 208 clin. samples against an available RIA, linear regression anal. gave a slope of 1.153, an intercept of 21.06, and a correlation coeff. of 0.813.

ST cyclosporin A deriv fluorescence polarization immunoassay

IT Proteins, properties
RL: PRP (Properties)
(pptn. of, with ammonium acetate and isopropanol)

IT Antibodies
RL: BIOL (Biological study)
(to cyclosporin A and metabolites, for fluorescence-polarization immunoassay)

IT Albumins, compounds
RL: BIOL (Biological study)
(conjugates, with cyclosporin A derivs., for antibody prodn.)

IT 122547-75-5
RL: PRP (Properties)
(conjugation of, with albumin)

IT 59865-13-3, Cyclosporin A 59865-13-3D, Cyclosporin A, metabolites
RL: ANT (Analyte); ANST (Analytical study)
(detn. of, by fluorescence polarization immunoassay)

IT 83602-41-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(oxidn. of, with osmium tetraoxide and periodate in albumin-cyclosporin A deriv. conjugate prepn.)
IT 122547-79-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and conjugation with albumin)
IT 122575-49-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, for fluorescence polarization immunoassay for cyclosporin A)
IT 121584-52-9P 122547-77-7P 122547-78-8P 122547-80-2P 122547-81-3P
122547-82-4P 122547-83-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, in albumin-cyclosporin A deriv. conjugate prepn.)
IT 122547-84-6P **122547-85-7P 122547-86-8P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, in cyclosporin A-aminomethylfluorescein conjugate prepn.)
IT 67-63-0, Isopropanol, biological studies
RL: BIOL (Biological study)
(protein pptn. with ammonium acetate and)
IT 631-61-8, Ammonium acetate
RL: BIOL (Biological study)
(protein pptn. with isopropanol and)
IT 122547-74-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, in prepn. of albumin-cyclosporin A deriv. conjugate)
IT 2921-14-4, Carboxymethoxylamine hemihydrochloride 122547-87-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with cyclosporin A deriv.)

L44 ANSWER 20 OF 29 HCAPLUS COPYRIGHT 2002 ACS
AN 1989:450102 HCAPLUS
DN 111:50102
TI Comparison of the in vitro immunosuppressive effects of cyclosporin A and its metabolites
AU Copeland, K. R.; Yatscoff, R. W.; Rush, D.; Jeffery, J. R.
CS Dep. Clin. Chem., Health Sci. Clin. Res. Cent., Winnipeg, MB, R3A 1R9, Can.
SO Transplantation Proceedings (**1989**), 21(1, Book 2), 1449-52
CODEN: TRPPA8; ISSN: 0041-1345
DT Journal
LA English
CC 1-7 (Pharmacology)
AB Five cyclosporin A (I) metabolites were isolated from I-treated kidney and liver transplant patients' urine and bile, resp., and tested for their immunosuppressive activity singly as well as in combination with I. A mixed lymphocyte system was used to test the immunosuppressant activity. All the 5 metabolites (M-17, M-18, M-8, M-26, and M-203-218) exhibited immunosuppressant activity, but at a significantly lower level than that by I.,. M-17, the major metabolite found in human blood, was .apprx.10% as active as I. Additive, but not synergistic, effects were obsd. when these metabolites were combined with I. The metabolites were isolated by using semipreparative HPLC and their structure confirmed by mass and NMR spectroscopy.
ST immunosuppression cyclosporin A metabolite
IT Immunosuppressants
(cyclosporin A and metabolites as)
IT Lymphocyte
(cyclosporin A and metabolites effect on human, immunosuppression in relation to)
IT 89270-26-8 89270-28-0, M17 89270-29-1, M-18 **100364-58-7**
107335-28-4, M 26

RL: BIOL (Biological study)
(cyclosporin A metabolite, immunosuppressant activity of, in human lymphocytes)
IT 59865-13-3, Cyclosporin A
RL: BIOL (Biological study)
(immunosuppression by, in human lymphocytes, metabolites in relation to)

L44 ANSWER 21 OF 29 HCAPLUS COPYRIGHT 2002 ACS
AN 1989:107532 HCAPLUS
DN 110:107532
TI Distribution of cyclosporin A metabolites among plasma and cells in whole blood: effect of temperature, hematocrit, and metabolite concentration
AU Lensmeyer, Gary L.; Wiebe, Donald A.; Carlson, Ian H.
CS Dep. Pathol., Univ. Wisconsin Hosp., Madison, WI, 53792, USA
SO Clinical Chemistry (Washington, DC, United States) (**1989**), 35(1), 56-63
CODEN: CLCHAU; ISSN: 0009-9147
DT Journal
LA English
CC 1-2 (Pharmacology)
AB Drug-free whole-blood samples supplemented with the cyclosporins and samples from transplant patients receiving cyclosporin A (CsA) were equilibrated at 4, 22, and 37.degree. for 2.5 h; the plasma and cells were sepd., and the fractions were assayed by HPLC. Partitioning of CsA and metabolites among plasma and cells was diverse and not always predictable in the patients' samples. Overall, although widely variable, >50% of the total concn. of metabolites M1, M8, M9, M10, M16, M17, U1, U8, and U9 in whole blood was assocd. with the cells, whereas >50% of M13, M18, M21, M25, M26, M203-218, U2, U3, U4, U5, and U7 was assocd. with plasma. A decrease in hematocrit from 47.8% to 24%, an increase of the sample's temp. (from 4 to 37.degree.), or an increase in analyte concn. (usually >500 .mu.g/L for selected metabolites) increased the relative portion assocd. with plasma in a nonlinear fashion. Parent CsA was most influenced by these changes; its relative concns. in plasma varied from 18% to 50%. These data support the preferential use of whole blood for therapeutic monitoring of cyclosporins.
ST cyclosporin A metabolite distribution plasma cell
IT Blood plasma
(cyclosporin A metabolites in human)
IT 59865-13-3, Cyclosporin A
RL: PROC (Process)
(distribution of, among blood plasma and cells in humans)
IT 59865-13-3D, Cyclosporin A, metabolites
RL: PROC (Process)
(distribution of, among blood plasma and cells, in humans)
IT 89270-23-5 89270-25-7 89270-26-8 89270-27-9 89270-28-0
89270-29-1 89288-32-4 **100364-58-7** 107335-27-3 107335-28-4
119386-81-1
RL: PROC (Process)
(distribution of, as cyclosporin A metabolite, among blood plasma and cells in humans)

L44 ANSWER 22 OF 29 HCAPLUS COPYRIGHT 2002 ACS
AN 1988:485582 HCAPLUS
DN 109:85582
TI Deposition of nine metabolites of cyclosporine in human tissues, bile, urine, and whole blood
AU Lensmeyer, Gary L.; Wiebe, D. A.; Carlson, I. H.
CS Dep. Pathol., Univ. Wisconsin Hosp., Madison, WI, USA
SO Transplantation Proceedings (**1988**), 20(2, Suppl. 2), 614-22
CODEN: TRPPA8; ISSN: 0041-1345
DT Journal

LA English
CC 1-1 (Pharmacology)
AB Cyclosporine (CsA) and 9 metabolites were detd. in human bile, urine, blood, and tissues by HPLC with a Bond Elut cyanopropyl extn. cartridge, a Zorbax CN column, a mobile phase of H2O-MeCN-tetrahydrofuran-HOAc-n-butylamine (610:375:20:0.16:0.1), and detection of 214 nm. The coeff. of variance was <10% and the precision for CsA in fat was 7.2% at 2290 .mu.g/kg. Several of the metabolites were found at concns. exceeding those of CsA in bile, urine, blood, and most tissues, except fat and pancreas. The HPLC profiles for CsA and metabolites in urine and blood were different.
ST cyclosporine metabolite blood urine tissue HPLC; liq chromatog cyclosporine metabolite
IT Bile
Blood analysis
Urine analysis
(cyclosporine and metabolites detn. in human, by HPLC)
IT Adipose tissue, composition
Brain, composition
Kidney, composition
Liver, composition
Lung, composition
Lymph gland
Muscle, composition
Pancreas, composition
Spleen, composition
(cyclosporine and metabolites of human, detn. of, by HPLC)
IT Chromatography, column and liquid
(high-performance, cyclosporine and metabolites detn. by, in human tissues)
IT 59865-13-3 89270-25-7 89270-26-8 89270-28-0 89270-29-1
**100364-58-7** 107335-27-3 107335-28-4
RL: ANT (Analyte); ANST (Analytical study)
(detn. of, as cyclosporine metabolite, in human tissues, by HPLC)
IT 59865-13-3, Cyclosporin A 59865-13-3D, Cyclosporin A, metabolites
RL: ANT (Analyte); ANST (Analytical study)
(detn. of, in human tissues, by HPLC)

L44 ANSWER 23 OF 29 HCAPLUS COPYRIGHT 2002 ACS
AN 1988:485581 HCAPLUS
DN 109:85581
TI Measurement of cyclosporine and 18 metabolites in blood, bile, and urine by high-performance liquid chromatography
AU Christians, U.; Schlitt, H. J.; Bleck, J. S.; Schiebel, H. M.; Kownatzki, R.; Maurer, G.; Strohmeyer, S. S.; Schottmann, R.; Wonigeit, K.; et al.
CS Zent. Biochem., Med. Hochsch., Hannover, Fed. Rep. Ger.
SO Transplantation Proceedings (**1988**), 20(2, Suppl. 2), 609-13
CODEN: TRPPA8; ISSN: 0041-1345
DT Journal
LA English
CC 1-1 (Pharmacology)
AB Cyclosporine (CsA), 11 known metabolites, and 7 unknown metabolites were detd. in human blood, bile and urine by HPLC. The blood samples were treated with MeCN-H2O (pH 3.0), cyclosporin D was added as an internal std., and the compds. were extd. on a column contg. octyl sorbent with CH2Cl2 as eluent. The CH2Cl2 was evapd. and the compds. were reconstituted in a mobile phase of MeCN-H2O (pH 3.0) (50:50). For urine samples, the internal std. and 250 .mu.L MeCN were added per mL of urine followed by the same extn. procedure. Bile, 500 mL, was mixed with CH2Cl2, 500 mL, the CH2Cl2 was evapd., and the residue was taken up into 150 mL MeCN-H2O and washed with hexane. Six mL of the aq. layer and 3 mL H2O were mixed and passed through the column. The CH2Cl2 was evapd. and the residue was take up into the mobile phase as above. Three of the new

metabolites had immunosuppressive effects in mixed lymphocyte cultures and in anti-CD3-stimulated lymphocyte assays. None of the metabolites had nonspecific toxicity in Epstein-Barr virus-transformed B-cells.

ST immunosuppression cyclosporine metabolite; cyclosporine metabolite blood bile urine HPLC; liq chromatog cyclosporine metabolite

IT Bile
Blood analysis
Urine analysis
(cyclosporine and metabolites detn. in human, by HPLC)

IT Immunosuppressants
(cyclosporine metabolites)

IT Toxicity
(of cyclosporine metabolites)

IT Chromatography, column and liquid
(high-performance, cyclosporine and metabolites detn. by, in human bile and blood and urine)

IT 59865-13-3 89270-25-7 89270-26-8 89270-27-9 89270-28-0
89270-29-1 89288-32-4 **100364-58-7** 107335-27-3 107335-28-4
RL: ANT (Analyte); ANST (Analytical study)
(detn. of, as cyclosporine metabolite, in human bile and blood and urine, by HPLC)

IT 59865-13-3, Cyclosporin A 59865-13-3D, Cyclosporin A, metabolites
RL: ANT (Analyte); ANST (Analytical study)
(detn. of, in human bile and blood and urine, by HPLC)

L44 ANSWER 24 OF 29 HCAPLUS COPYRIGHT 2002 ACS
AN 1988:142677 HCAPLUS
DN 108:142677
TI Liquid-chromatographic measurement of cyclosporin A and its metabolites in blood, bile, and urine
AU Christians, U.; Zimmer, K. O.; Wonigeit, K.; Maurer, G.; Sewing, K. F.
CS Abt. Allg. Pharmakol., Med. Hochsch. Hannover, Hannover, D-3000/61, Fed. Rep. Ger.
SO Clinical Chemistry (Washington, DC, United States) (**1988**), 34(1), 34-9
CODEN: CLCHAU; ISSN: 0009-9147
DT Journal
LA English
CC 1-1 (Pharmacology)
AB Cyclosporin A and its metabolites were detd. in the blood, bile, and urine of humans by using solid-phase extn. columns and HPLC. To facilitate calcns. of concns. of cyclosporin A and its metabolites from the chromatograms, cyclosporin D was used as internal std. For the HPLC 2 sequential 250-mm anal. columns filled with reversed-phase octyl (C8) sorbent were used. Elution was done with a concave gradient of water, adjusted to pH 3.0 with H3PO4 and MeCN. Peaks were detected at 205 nm. For characterization of the chromatog. peaks, the authors isolated, by semi-preparative HPLC, 32 fractions representing peaks potentially related to cyclosporin A metabolites and reinjected them into the HPLC system under the same conditions as authentic cyclosporin A metabolites. Anal. recovery was 70-80%. The inter-assay coeffs. of variations for bile and urine were 7.2 and 12.3%, resp. The method was used for routine monitoring of cyclosporin A and its metabolites.

ST cyclosporin A metabolite detn HPLC; liq chromatog cyclosporin A metabolite; bile cyclosporin A metabolite HPLC; urine cyclosporin A metabolite HPLC; blood cyclosporin A metabolite HPLC

IT Bile
Blood analysis
Urine analysis
(cyclosporin A and its metabolites detn. in human, by HPLC)

IT 89270-23-5 89270-24-6 89270-25-7 89270-26-8 89270-27-9
89270-28-0 89270-29-1 89288-32-4 **100364-58-7** 107335-27-3
107335-28-4

RL: ANT (Analyte); ANST (Analytical study)
(detn. of, in body fluid of humans, as cyclosporin A metabolite by HPLC)

IT 59865-13-3, Cyclosporin A 59865-13-3D, Cyclosporin A, metabolites
RL: ANT (Analyte); ANST (Analytical study)
(detn. of, in body fluid of humans, by HPLC)

L44 ANSWER 25 OF 29 HCAPLUS COPYRIGHT 2002 ACS
AN 1988:15717 HCAPLUS
DN 108:15717
TI The in vitro activity, radioimmunoassay cross-reactivity, and molecular weight of thirteen rabbit cyclosporine metabolites
AU Hartman, N. R.; Jardine, I.
CS Dep. Pharmacol., Mayo Clin., Rochester, MN, 55905, USA
SO Drug Metabolism and Disposition (**1987**), 15(5), 661-4
CODEN: DMDSAI; ISSN: 0090-9556
DT Journal
LA English
CC 1-2 (Pharmacology)
AB Thirteen metabolites of cyclosporine were isolated from the bile of rabbits receiving i.v. cyclosporine. The mol. wts. of these metabolites were detd. by fast atom bombardment mass spectrometry. These mol. wts. were consistent with hydroxylated, N-demethylated, and carboxylated metabolites of cyclosporine as described previously. The in vitro activities of the metabolites were established using mitogen-stimulated lymphocyte proliferation assays. Only the two monohydroxylated metabolites were found to have significant activity, this being between 5 and 10% of that of the parent drug. The metabolites were also compared with cyclosporine in two com. radioimmunoassay kits. The metabolites were found to cross-react with the parent drug in amts. ranging 20-100%, with the least polar metabolites cross-reacting the most strongly. It is concluded that the cross-reacting metabolites measured by the presently available radioimmunoassays for cyclosporine probably do not represent significant addnl. immunosuppressive activity in vivo.
ST cyclosporine metabolite mol wt immunosuppression; RIA cross reactivity cyclosporine metabolite
IT Immunosuppression
(by cyclosporine metabolites)
IT Molecular weight
(of cyclosporine metabolites)
IT Immunochemical analysis
(radioimmunoassay, cross reactivity, for cyclosporine metabolites and parent drug)
IT 89270-25-7 89270-26-8 89270-28-0 **100364-58-7** 112077-93-7
RL: PRP (Properties)
(isolation and mol. wt. of, as cyclosporine metabolite, immunosuppressive activity and RIA cross-reactivity in)
IT 59865-13-3D, Cyclosporine, metabolites
RL: PRP (Properties)
(isolation and mol. wt. of, immunosuppressive activity and RIA cross-reactivity in)

L44 ANSWER 26 OF 29 HCAPLUS COPYRIGHT 2002 ACS
AN 1988:15665 HCAPLUS
DN 108:15665
TI Identification and analysis of nine metabolites of cyclosporine in whole blood by liquid chromatography. 2: Comparison of patients' results
AU Lensmeyer, Gary L.; Wiebe, Donald A.; Carlson, Ian H.
CS Dep. Pathol. Lab. Med., Univ. Wisconsin, Madison, WI, 53792, USA
SO Clinical Chemistry (Washington, DC, United States) (**1987**), 33(10), 1851-5
CODEN: CLCHAU; ISSN: 0009-9147
DT Journal

LA English
CC 1-1 (Pharmacology)
AB A HPLC assay [for parent cyclosporine (CsA) and nine metabolites] and a radioimmunoassay were used to detail the diversity of results among whole-blood samples from patients with transplanted organs. Results by HPLC vs RIA for CsA or for individual metabolites vs CsA (or RIA) were diverse, with correlation coeffs. (r) ranging from 0.058 to 0.933. RIA vs HPLC (sum of CsA + metabolites) gave the best comparison (slope = 0.931, yr-intercept 14 .mu.g/L, r = 0.933); but the scatter of data about the regression line remained significant (Sy/x = 132 .mu.g/L). Most important, RIA/HPLC(CsA) vs HPLC(sum of metabolites) was remarkably poor (r = 0.222). A 12-h pharmacokinetic curve (for drug concns. in a heart-transplant patient) displayed dissimilar times for peak concns. of CsA and metabolites; each differed in the proportion (48% to 81% of peak concn.) eliminated from blood over the 12 h. These studies exemplify the utility of a more-inclusive, specific assay to monitor the diverse disposition of cyclosporines in patients and to demonstrate the errors assocd. with use of the RIA/HPLC ratio technique to predict metabolite concns.
ST cyclosporine metabolite blood HPLC RIA; liq chromatog radioimmunoassay cyclosporine metabolite blood
IT Blood analysis
(cyclosporine and metabolites detn. in human, by HPLC vs. RIA)
IT Chromatography, column and liquid
(high-performance, cyclosporine and metabolites detn. in human blood by RIA vs.)
IT Immunochemical analysis
(radioimmunoassay, cyclosporine and metabolites detn. in human blood by HPLC vs.)
IT 59865-13-3, Cyclosporin A 59865-13-3D, Cyclosporin A, metabolites 89270-25-7 89270-26-8 89270-28-0 **100364-58-7**
RL: ANT (Analyte); ANST (Analytical study)
(detn. of, in human blood, by HPLC vs. RIA)

L44 ANSWER 27 OF 29 HCAPLUS COPYRIGHT 2002 ACS
AN 1988:15664 HCAPLUS
DN 108:15664
TI Identification and analysis of nine metabolites of cyclosporine in whole blood by liquid chromatography. 1: Purification of analytical standards and optimization of the assay
AU Lensmeyer, Gary L.; Wiebe, Donald A.; Carlson, Ian H.
CS Dep. Pathol. Lab. Med., Univ. Wisconsin, Madison, WI, 53792, USA
SO Clinical Chemistry (Washington, DC, United States) (**1987**), 33(10), 1841-50
CODEN: CLCHAU; ISSN: 0009-9147
DT Journal
LA English
CC 1-1 (Pharmacology)
AB An extn. and an isocratic HPLC sepn. of cyclosporine (CsA) and nine metabolites (M1, M8, M17, M18, M21, M25, M26, M203-218, and MUNDF1) from whole blood are described. Metabolites (for stds.) were purified from human bile with liq.-liq. and solid-phase extns., chromatographed on a cyanopropyl (CN) semipreparative HPLC column, and further purified on octyl, CN, and silica columns. The identity of each metabolite was verified with authentic stds. on three chem. different HPLC columns and on the basis of cross-reactivity data from radioimmunoassay. For the routine anal. method, 1 mL of whole blood is dild., hemolyzed, and applied to a Bond Elut CN (500 mg) cartridge to ext. CsA, metabolites, and cyclosporin C, the internal std. Interferences are removed by using four wash solns. and an addnl. cartridge of octyldecyl sorbent introduced prior to elution. Analytes are sepd. on a Zorbax CN anal. column maintained at 58s, with detection of 214 nm. Anal. recovery, as tested with three lots of CN sorbent, ranged 47-95% for the 10 cyclosporines. Between-run coeffs. of

variation are <10% at 200 .mu.g/L (concn. of each compd.) and the std. curves are linear to 1500 .mu.g/L. A study of the sepn. mechanisms are reported.
ST cyclosporine metabolite blood HPLC; liq chromatog cyclosporine metabolite blood
IT Blood analysis
(cyclosporine and metabolites detn. in human, by HPLC)
IT Bile
(cyclosporine metabolites purifn. from human)
IT Chromatography, column and liquid
(high-performance, of cyclosporine and metabolites in human blood)
IT 59865-13-3, Cyclosporine A 59865-13-3D, Cyclosporin A, metabolites 89270-23-5 89270-25-7 89270-26-8 89270-28-0 89270-29-1 **100364-58-7** 107335-27-3 107335-28-4
RL: ANT (Analyte); ANST (Analytical study)
(detn. of, in human blood by HPLC)

L44 ANSWER 28 OF 29 HCAPLUS COPYRIGHT 2002 ACS
AN 1986:564395 HCAPLUS
DN 105:164395
TI Mass spectrometric analysis of cyclosporine metabolites
AU Hartman, N. R.; Jardine, I.
CS Dep. Pharmacol., Mayo Clin., Rochester, MN, 55905, USA
SO Biomedical & Environmental Mass Spectrometry (**1986**), 13(7), 361-72
CODEN: BEMSEN; ISSN: 0887-6134
DT Journal
LA English
CC 1-2 (Pharmacology)
AB Sensitive mass spectrometric techniques were developed to det. the structure of metabolites of cyclosporine (CsA) [59865-13-3]. First, the mol. wt. of the metabolite was detd. by using fast atom bombardment mass spectrometry or thermospray liq. chromatog./mass spectrometry. The metabolite is then hydrolyzed to its component amino acids, which were esterified and acylated and identified by gas chromatog./mass spectrometry. To distinguish metab. at the 4 identical N-Me leucines, the metabolite was partially hydrolyzed, the resulting peptides were derivatized to the trimethylsilylpolyamino alcs., and these in turn were analyzed by gas chromatog./mass spectrometry. These procedures were used to det. the structure of metabolites of CsA isolated from rabbit bile. The detn. of the structure of one metabolite carboxylated on the .eta.-carbon of amino acid 1, and of one metabolite hydroxylated on the .eta.-carbon of amino acid 1 and on the .gamma.-carbon of N-Me leucine 9 is presented. These procedures should be generally useful for the structural anal. of microgram amts. of CsA metabolites and analogs.
ST cyclosporine metab bile mass spectrometry; mass spectrometry cyclosporine metabolite
IT Bile
(cyclosporine metab. by)
IT 89270-24-6 89270-26-8 89270-28-0 **100364-58-7**
RL: BIOL (Biological study)
(as cyclosporine metabolite, structure elucidation by mass spectrometry of)
IT 89270-25-7 104671-68-3 104671-69-4 104671-70-7 104696-98-2
RL: PRP (Properties)
(mass spectra of)
IT 59865-13-3
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metab. of, by bile, metabolite structure detn. by mass spectrometry after)

L44 ANSWER 29 OF 29 HCAPLUS COPYRIGHT 2002 ACS

AN 1986:81480 HCAPLUS
DN 104:81480
TI An acid metabolite of cyclosporine
AU Hartman, Neil R.; Trimble, Laird A.; Vederas, John C.; Jardine, Ian
CS Dep. Pharmacol., Mayo Clin., Rochester, NY, 55905, USA
SO Biochemical and Biophysical Research Communications (**1985**), 133(3), 964-71
CODEN: BBRCA9; ISSN: 0006-291X
DT Journal
LA English
CC 1-2 (Pharmacology)
AB The primary biliary metabolite of cyclosporine (I) was isolated from rabbit and human bile. The material was identified by mass spectrometry and by NMR spectrometry as the .alpha.,.beta.-unsatd. carboxylic acid I deriv. [**100364-58-7**] in which the N-Me group of the cyclosporine-specific 9 C amino acid is oxidized to an .alpha., .beta. unsatd. carboxylic acid functionality. This major cyclosporine metabolite is inactive in a phytohemagluttinin-stimulated lymphocyte proliferation assay.
ST cyclosporine metabolite identification spectrometry NMR; bile cyclosporine metabolite
IT Bile
(cyclosporine metabolite detn. in, of humans and lab. animals, by mass spectrometry and NMR)
IT Immunosuppression
(cyclosporine metabolite in relation to)
IT **100364-58-7**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(as cyclosporine metabolite, in bile of humans and lab. animals, identification and activity of)

=> fil uspatall
FILE 'USPATFULL' ENTERED AT 15:35:10 ON 12 DEC 2002
CA INDEXING COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPAT2' ENTERED AT 15:35:10 ON 12 DEC 2002
CA INDEXING COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)

=>
=> d bib abs hitrn tot l45

L45 ANSWER 1 OF 3 USPATFULL
AN 2002:259374 USPATFULL
TI Cyclosporins for the treatment of respiratory diseases
IN Or, Yat Sun, Cambridge, MA, UNITED STATES
Lazarova, Tsvetelina, Brookline, MA, UNITED STATES
PI US 2002142946 A1 20021003
AI US 2001-800856 A1 20010305 (9)
DT Utility
FS APPLICATION
LREP SANDHYA L. KALKUNTE, ENANTA PHARMACEUTICALS, INC., 500 ARSENAL STREET, WATERTOWN, MA, 02472
CLMN Number of Claims: 11
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 945
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to novel semisynthetic cyclosporin analogs of Formula (I): ##STR1##

X is absent, --C1-C6 alkyl-, or --C3-C6 cycloalkyl-

Y is selected from the group consisting of:

(i) C(O)--O--R1, where R1 is hydrogen, C1-C6 alkyl, optionally substituted with halogen, heterocyclic, aryl, C1-C6 alkoxy, C1-C6 alkylthio, halogen-substituted C1-C6 alkoxy, or halogen-substituted C1-C6 alkylthio;

(ii) C(O)--S--R1, where R1 is as previously defined;

(iii) C(O)--OCH.sub.2--OC(O)R2, where R2 is C1-C6 alkyl, optionally substituted with halogen, C1-C6 alkoxy; C1-C6 alkylthio, heterocyclic or aryl;

(iv) C(S)--O--R1, where R1 is as previously defined, and

(v) C(S)--S--R1, where R1 is as previously defined;

B is -.alpha.Abu-, -Val-, -Thr- or -Nva-; and

U is -(D)Ala-, -(D)Ser-, --[O--(2-hydroxyethyl)(D)Ser]-, --[O-acyl(D)Ser]- or --[O--(2-acyloxyethyl)(D)Ser]-.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **100364-58-7P 457612-98-5P 457612-99-6P**
**457613-00-2P 457613-01-3P 457613-02-4P**
**457613-03-5P 457613-04-6P 457613-05-7P**
**457613-06-8P 457613-07-9P 457613-08-0P**
**457613-09-1P 457613-10-4P 457613-11-5P**
(cyclosporins for the treatment of respiratory diseases)
IT **122547-85-7P**
(cyclosporins for the treatment of respiratory diseases)

L45 ANSWER 2 OF 3 USPATFULL
AN 95:58066 USPATFULL
TI Fluorescence polarization assay for cyclosporin A and metabolites and related immunogens and antibodies
IN Wang, Nai-Yi, Mundelein, IL, United States
Wang, Philip P., Libertyville, IL, United States
Morrison, Marjorie A., Grayslake, IL, United States
PA Abbott Laboratories, Abbott Park, IL, United States (U.S. corporation)
PI US 5427960 19950627
AI US 1994-318570 19941005 (8)
RLI Continuation of Ser. No. US 1993-60598, filed on 12 May 1993, now abandoned which is a division of Ser. No. US 1991-776890, filed on 15 Oct 1991, now patented, Pat. No. US 5239057 which is a continuation of Ser. No. US 1989-376244, filed on 6 Jul 1989, now abandoned which is a continuation of Ser. No. US 1987-31494, filed on 27 Mar 1987, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Chan, Christina Y.
CLMN Number of Claims: 3
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 810
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention is directed to a fluorescence polarization immunoassay for cyclosporin A and metabolites thereof. The present invention also relates to novel cyclosporin A derivative compounds useful in fluorescence polarization techniques. Included among the novel compounds are cyclosporin A derivatives where the amino acid in the

first position is altered. The cyclosporin A derivatives are useful in forming immunogens for raising antibodies specific to cyclosporin A and metabolites thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **122547-85-7P 122547-86-8P**
(prepn. of, in cyclosporin A-aminomethylfluorescein conjugate prepn.)

L45 ANSWER 3 OF 3 USPATFULL
AN 93:69983 USPATFULL
TI Fluorescence polarization assay for cyclosporin a and metabolites and related immunogens and antibodies
IN Wang, Nai-Yi, Mundelein, IL, United States
Wang, Philip P., Libertyville, IL, United States
Morrison, Marjorie A., Grayslake, IL, United States
PA Abbott Laboratories, Abbott Park, IL, United States (U.S. corporation)
PI US 5239057 19930824
AI US 1991-776890 19911015 (7)
RLI Continuation of Ser. No. US 1989-376244, filed on 6 Jul 1989, now abandoned which is a continuation of Ser. No. US 1987-31494, filed on 27 Mar 1987, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Chan, Y. Christina
LREP Steele, Gregory W., Pope, Lawrence S., Breininger, Thomas M.
CLMN Number of Claims: 7
ECL Exemplary Claim: 5
DRWN No Drawings
LN.CNT 771
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention is directed to a fluorescence polarization immunoassay for cyclosporin A and metabolites thereof. The present invention also relates to novel cyclosporin A derivative compounds useful in fluorescence polarization techniques. Included among the novel compounds are cyclosporin A derivatives where the amino acid in the first position is altered. The cyclosporin A derivatives are useful in forming immunogens for raising antibodies specific to cyclosporin A and metabolites thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **122547-85-7P 122547-86-8P**
(prepn. of, in cyclosporin A-aminomethylfluorescein conjugate prepn.)

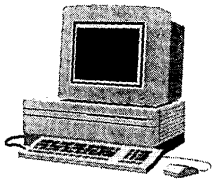
=> d his

(FILE 'HCAPLUS' ENTERED AT 14:18:09 ON 12 DEC 2002)
DEL HIS
E OR Y/AU
L1 105 S E4-E8
E LAZAROVA T/AU
L2 30 S E3-E11
E ENANTA/PA,CS
L3 13 S E3-E9
L4 137 S L1-L3
L5 5 S L4 AND ?CYCLOSPOR?
SEL DN AN 1 2
L6 2 S L5 AND E1-E4
SEL RN

FILE 'REGISTRY' ENTERED AT 14:21:00 ON 12 DEC 2002
L7 21 S E5-E25
L8 17 S L7 AND SQL/FA

```
L9              STR
L10          32 S L9
L11         685 S L9 FUL
                SAV L11 LIU800/A
L12         727 S ['ABU''NVA'VT]'SAR'LVLA[AS]LLV/SQSP
L13         342 S L11 AND L12
L14         342 S L13 AND 11/SQL
L15             STR L9
L16          11 S L15 CSS SAM SUB=L14
L17         224 S L15 CSS FUL SUB=L14
                SAV L17 LIU800A/A
L18             STR L15
L19           9 S L18 CSS SAM SUB=L17
L20         166 S L18 CSS FUL SUB=L17
                SAV L20 LIU800B/A
L21             STR L9
L22             STR L21
L23           0 S L22 SAM SUB=L20
L24           2 S L22 FUL SUB=L20
                STR L22
L26         126 S L25 FUL SUB=L20
                SAV L26 LIU800C/A
L27          11 S L26 AND (LABELED OR IDS/CI OR (D OR T)/ELS OR 11C# OR 13C# OR
L28         115 S L26 NOT L27
L29          27 S L28 AND NC>=2
L30          21 S L28 AND NR>=3
L31          82 S L28 NOT L29,L30
L32           1 S L31 AND MULTICHAIN/NTE
L33          81 S L31 NOT L32
L34          65 S L33 NOT L8
L35          12 S L34 AND (C64H113N11O15 OR C69H114N12O17 OR C68H116N12O16 OR C
                SEL RN L35 2 5 7-12
L36           4 S L35 NOT E26-E33
                SEL RN 4
L37           3 S L36 NOT E34
L38          20 S L8,L37
                SAV L38 LIU800D/A

     FILE 'HCAOLD' ENTERED AT 15:32:02 ON 12 DEC 2002
L39           0 S L38

     FILE 'USPATFULL, USPAT2' ENTERED AT 15:32:05 ON 12 DEC 2002

     FILE 'REGISTRY' ENTERED AT 15:32:24 ON 12 DEC 2002
                SEL RN L8 17
L40          16 S L8 NOT E35

     FILE 'HCAPLUS' ENTERED AT 15:32:57 ON 12 DEC 2002.
L41          29 S L40 OR L37
L42           1 S L41 AND L4
L43          28 S L41 AND (PD<=20010305 OR PRD<=20010305 OR AD<=20010305)
L44          29 S L41-L43

     FILE 'USPATFULL, USPAT2' ENTERED AT 15:33:58 ON 12 DEC 2002
L45           3 S L40 OR L37

     FILE 'REGISTRY' ENTERED AT 15:34:17 ON 12 DEC 2002

     FILE 'HCAPLUS' ENTERED AT 15:34:49 ON 12 DEC 2002

     FILE 'USPATFULL, USPAT2' ENTERED AT 15:35:10 ON 12 DEC 2002
```

# BioTech-Chem Library
## Search Results
## Feedback Form (Optional)



Scientific & Technical Information Center

The search results generated for your recent request are attached. If you have any questions or comments (compliments or complaints) about the scope or the results of the search, please contact ***the BioTech-Chem searcher*** who conducted the search ***or contact***:

**Mary Hale, Supervisor, 308-4258**
CM-1 Room 1E01

---

### *Voluntary Results Feedback Form*

- *I am an examiner in Workgroup:* *(Example: 1610)*
- *Relevant prior art **found**, search results used as follows:*
  - ☐ 102 rejection
  - ☐ 103 rejection
  - ☐ Cited as being of interest.
  - ☐ Helped examiner better understand the invention.
  - ☐ Helped examiner better understand the state of the art in their technology.

  *Types of relevant prior art found:*
  - ☐ Foreign Patent(s)
  - ☐ Non-Patent Literature
    (journal articles, conference proceedings, new product announcements etc.)
- *Relevant prior art **not found**:*
  - ☐ Results verified the lack of relevant prior art (helped determine patentability).
  - ☐ Search results were not useful in determining patentability or understanding the invention.

**Other Comments:**

---

Drop off completed forms at the **Circulation Desk CM-1,** or send to Mary Hale, **CM1-1E01 or e-mail mary.hale@uspto.gov.**